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SCIENCE FOR THE CURIOUS

# Discover®

September 2015

# A City's Buried Secrets

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One of 3,000 skeletons found during a London railway dig.

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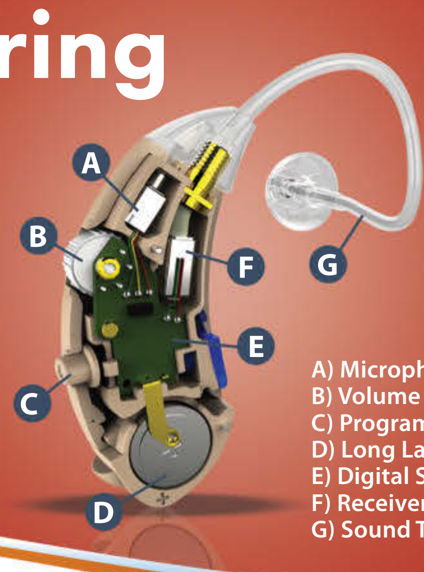


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BY ADAM HADHAZY

Earth-like planets, similar to the one illustrated here, are plentiful in the Milky Way and could help researchers find other livable worlds.

MARK A. GARLICK/MARKGARLICK.COM

**ON THE COVER** *Photo by Justin Tallis/AFP/Getty Images*

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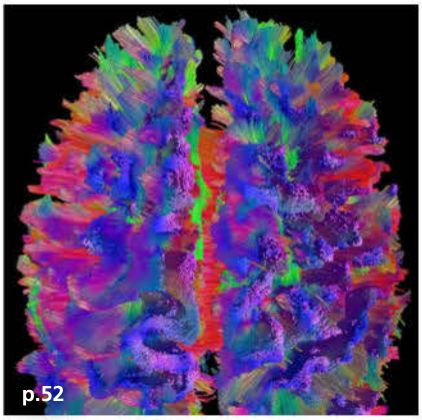
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TOP: ISTANBUL UNIVERSITY YENIKAPI SHIPWRECKS PROJECT ARCHIVE. BOTTOM: WALTER SCHNEIDER LABORATORY

## Editor's Note

# Moment of Wonder

**A simple stone could rock your world.**

When I was 12, I spent a hot summer day digging up a rock in my yard. It kept dinging my mower blade, and I was sick of it. But annoyance quickly turned to fascination as I realized that this rock was rectangular, with beveled edges. Its placement there at the edge of our old cobbled driveway was no accident of nature.

*It's a gravestone*, I thought. In fact, it was a carriage step, a remnant of the 19th-century house that once stood on our land. A simple thing, that stone, but it rocked my world, filling me with a sense of discovery so profound that even now my stomach gets fluttery when I think of it.

It's that same way Ufuk Kocabaş must have felt as a child when he found his first artifact. Kocabaş, who led the dig of the ancient Byzantine port in his home city of Istanbul, will tell you all about it in our cover story, "Peeling Back a City's Layers" (page 28).

What's your moment of discovery? What science fact or finding has wowed you, filled you with a sense of wonder? Email me at editorial@discovermagazine.com and share it with me.

**NEXT ISSUE:** *Want to know how science will help us live better longer? Check out our big Science of Aging issue, coming in October. See you then!*

Stephen C. George, **EDITOR IN CHIEF**

## YOUR REPLY

Back in our June issue, I asked readers how far ahead they would go if they could visit the future, and what they would hope to see when they got there. Many of you want to go hundreds or thousands of years forward, but Anthony Rakoczy is prepared to go quite far ahead — about 4 billion years, in fact:

*To be there to see the Andromeda Galaxy as it merges with our Milky Way would be my greatest desire. To see the whole sky alight at night, from horizon to horizon, would be truly an event to witness.*

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WILLIAM ZUBACK/DISCOVER

# THE CRUX

## The Latest Science News & Notes

**LIGHTNING 'N' LAVA**

**After 43 years of slumber, the Calbuco volcano in southern Chile's Lake District erupted in a spectacular display of lightning, lava and hot ash, ejecting a plume 7 miles high and forcing thousands to evacuate. The friction of fast-moving ash particles from the volcano's vent created electric charges — and the ideal conditions for a "dirty thunderstorm" of lightning, researchers say. The phenomenon, still not fully understood, occurs soon after the initial eruption, when energy output peaks. Photographer Francisco Negroni was 27 miles away when he took this time exposure after dark, shortly after the blast in April. "The expulsion of the lava was like the sound of a jet engine," he recalls.**

— ERNIE MASTROIANNI; PHOTO BY FRANCISCO NEGRONI

# Snowstorm's End

## Remnants of a defunct Soviet space program gather dust and bird droppings in a Kazakhstan facility.

Inside a deteriorating hangar at the Baikonur Cosmodrome sit a pair of derelict spacecraft, built by the Soviet Union as part of a bold challenge to the U.S. manned space program. Only weeks before NASA's return to manned spaceflight in September 1988, more than two years after being grounded in the wake of the *Challenger* disaster, the Soviet space agency released photos of its own space shuttle. Named *Buran* ("snowstorm" in Russian), it looked almost identical to the American shuttle. On Nov. 15, 1988, *Buran* orbited Earth twice and made a nearly perfect landing without any humans on board. Money dried up after the Soviet Union's collapse in 1991, however, and it never flew again. Both shuttle programs are now defunct, and the remaining U.S. shuttles are on display in museums. *Buran* was destroyed in a 2002 building collapse at Baikonur; its siblings, pictured here, never left Earth. One was a non-flying replica used to test equipment. The other, dubbed *Ptichka* ("little bird"), was nearly 95 percent complete and intended for spaceflight. Ironically, the humble Russian-built Soyuz spacecraft, operational since the '60s, outlasted both programs and is currently the only ride for U.S. and Russian astronauts to reach the International Space Station. —ERNIE MASTROIANNI; PHOTOS BY RALPH MIREBS

Electronics and other equipment were tested for fit and function in the cockpit of the "test bed" replica spacecraft.

Tools and hardware, left behind decades ago as the program lost its funding, still clutter the test bed's cargo bay air lock.

A massive hangar with 140-foot-tall doors houses the derelict spacecraft at Baikonur Cosomodrome in Kazakhstan.

*Buran* lifted off from Baikonur on Nov. 15, 1988 (right), orbited Earth twice and landed successfully on autopilot. It never flew again, however, and the program ended in the early '90s from a lack of funding. *Buran* was destroyed in a 2002 building collapse; today, replicas and partly built vehicles from the project sit abandoned.

BOTTOM RIGHT: SOVFOTO/UIG VIA GETTY IMAGES

THE CRUX

# Trading Plates

A diet swap for just two weeks yields remarkable changes in low- and high-risk cancer groups.

By swapping beans for burgers (or vice versa), participants also traded their risk of colon cancer.

**Your body responds to changes** in what you eat — for better or worse — much faster than you might think. That's what researchers discovered during a recent study on the link between diet and colon cancer risk.

The project involved trading the typical diets of two groups: African-Americans, who are at high risk for colon cancer, and rural South Africans, who have a much lower risk for the disease. After two weeks of eating the high-fiber, low-fat and low-animal-protein South African diet, African-Americans in the study saw a significant decrease in inflammation and levels of several biomarkers considered predictive of colon cancer risk. At the same time, the South African participants' level of risk increased.

Shortly after the study was published in *Nature Communications*, lead investigator Stephen O'Keefe, a nutritional gastroenterologist at the University of Pittsburgh, chatted with *Discover*'s Gemma Tarlach about the findings.

**Q** *How are the biomarkers you studied associated with cancer risk?*

**A** The chief biomarker we studied was Ki67 epithelial cell [proteins]. Measuring that gives an indication of proliferation, or cell turnover. As Ki67 progressively increases, you see more neoplastic [or abnormal growth] conditions. If you can demonstrate a change in the proliferation rate, and a change in inflammation, you can show increased risk of cancer.

**Q** *What's the next step for this line of research?*

**A** We've shown that in high-risk populations, if you change to a high-fiber, low-fat, low-meat diet, mucosal biomarkers change in two weeks. But is it the high fiber, the low fat or the low meat component of the change? The next step is to single each out.

**Q** *I imagine that going from porridge and mango to hamburgers and mac 'n' cheese — or vice versa — was a shock to participants' taste buds. What did they think of the food?*

**A** Both diets were extremely well tolerated. That said, the African-American participants thought that perhaps there were too many beans on the menu (laughs). From an African point of view, when given the nasty Western diet, they loved it. In rural Africa, people don't eat Western food not because they don't want to, but because it's not available.

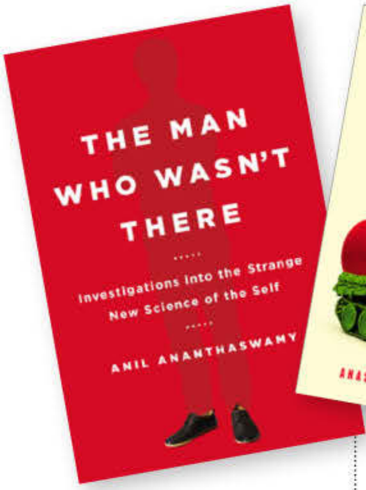
**Q** *There is a lot of research into whether obese individuals have different microbiota, or gut microbes, than people of normal weight. While your study was focused on colon cancer risk, several participants were obese, but there were no differences in microbiota between the obese and the normal weight individuals of their group. Was that a surprising find?*

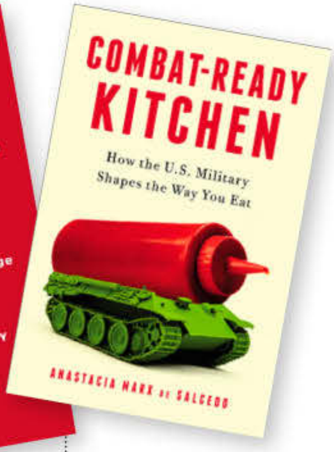
**A** No. A lot of changes in the microbiota are subtle, and a consequence of what you eat over a long period of time. You don't get obese overnight. It's a tremendously complicated field, which is why we've seen results all over the place when people look for the relationship between microbiota and obesity.

**Q** *Should anyone interested in reducing colon cancer risk adopt the study's rural South African diet?*

**A** I believe in whole foods and a balanced diet. But the African diet is really an impoverished diet. It's got what the Western diet is missing — fiber — and it doesn't have too much meat and fat, but it is not as rich in micronutrients and vitamins as the Western diet.

TOP: SHIRA RAZ/SHUTTERSTOCK. BOTTOM: EVA GRUENDEMANN/SHUTTERSTOCK




## COMBAT-READY KITCHEN

*By Anastacia Marx de Salcedo*

We thank NASA for powdery, vaguely citrus Tang, of course, but when was the last time you saluted the armed forces for the energy bar in your gym bag or the plastic wrap protecting last night's leftovers? In this engaging, wide-ranging investigation, food writer Salcedo reveals how yesterday's experiments in feeding combat troops have evolved into the convenience foods likely sitting on your pantry shelves. —GEMMA TARLACH

## THE MAN WHO WASN'T THERE

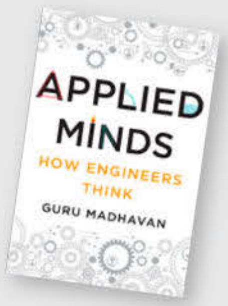
*By Anil Ananthaswamy*

At the center of this book is a question humans have asked for eons: Who am I? With a thoughtful touch, Ananthaswamy dives in to answer it. He introduces us to people facing radically altered senses of identity: an Alzheimer's patient whose life narrative erodes relentlessly; a woman whose schizophrenic world is filled with voices; a man who feels he must amputate his leg to feel whole. These individual stories become springboards into the biological — and philosophical — roots of our sense of self. In the end, the Buddhist tenet of letting go of the self might make the most sense of all. —BECKY LANG

## Other Pages We're Turning

### APPLIED MINDS: How Engineers Think

*By Guru Madhavan*




Biomedical engineer Madhavan delivers an accessible and very human story of innovators, from Alfred Hitchcock's thought process crafting *The Birds* to a father motivated by grief to improve emergency response times.

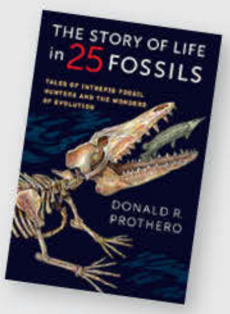
### SPIRALS IN TIME: The Secret Life and Curious Afterlife of Seashells

*By Helen Scales*


With the soul of a poet and a talent for finding the most intriguing trivia about familiar seaside sights, marine biologist Scales turns the mundane into the magical.

### THE STORY OF LIFE IN 25 FOSSILS

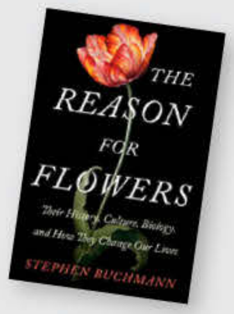
*By Donald Prothero*




From the humble first fossils known as *Cryptozoon* to the spectacular sea monster *Kronosaurus*, Prothero guides readers through the history of life on our planet, weaving in entertaining tales of how the fossils were discovered — and the scientific debates they often provoked.

### THE REASON FOR FLOWERS: Their History, Culture, Biology, and How They Change Our Lives

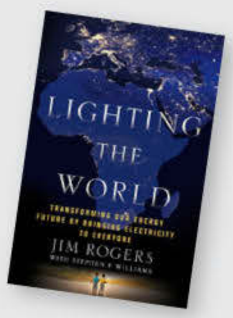
*By Stephen Buchmann*




Our love affair with blooming plants began with the earliest human ancestors. But by then, flowers already had played a critical role on the planet for millions of years, one brought to life in careful detail by pollination ecologist Buchmann.

### LIGHTING THE WORLD: Transforming Our Energy Future by Bringing Electricity to Everyone

*By Jim Rogers*

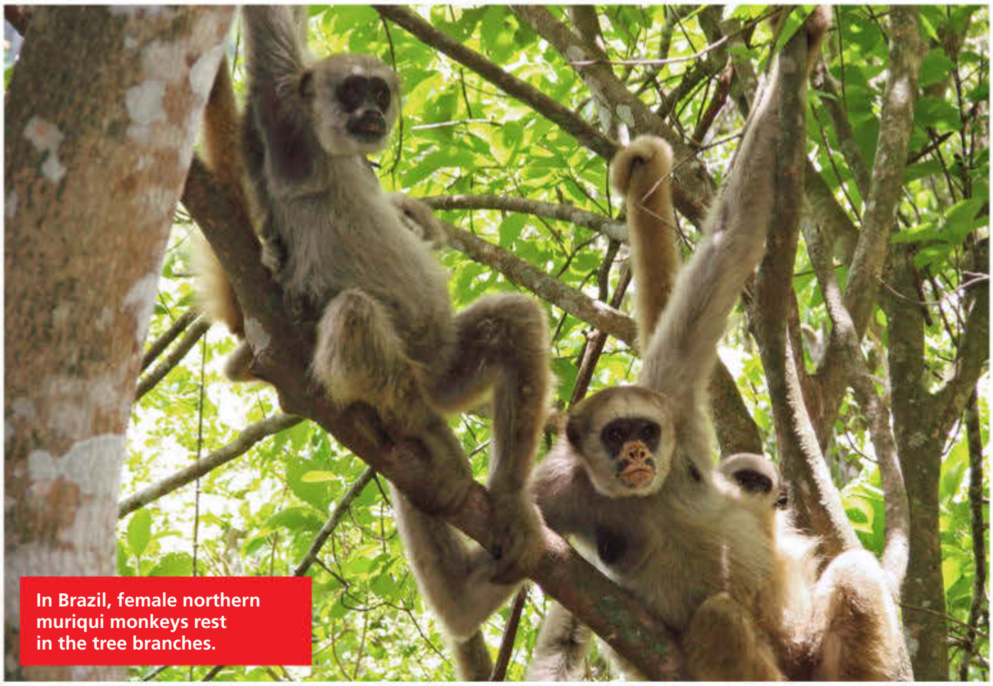



With the evangelizing feel of a TED talk, former energy exec Rogers makes his provocative case for powering up the Third World. —GEMMA TARLACH

# One of Us

A group of monkeys banded together to protect a fellow primate.

**In 1982, when University of Wisconsin** anthropologist Karen Strier saw her first northern muriqui in Brazil's Atlantic Forest, fewer than 1,000 of the critically endangered monkeys remained, scattered across a few remnant patches of forest. At the time, the primate — South America's largest — was assumed to be inherently aggressive and living in male-dominated groups. Strier's field studies would dispel that myth and reveal the monkeys were egalitarian and peaceful. But her dedication to the muriquis was forged in the forest long before she understood them fully. It was a moment in 1983, early in her first field season, after the group of males and females she was following had adjusted to her presence.



In Brazil, female northern muriqui monkeys rest in the tree branches.

University of Wisconsin anthropologist Karen Strier in Brazil's Atlantic Forest in 2013.

## IN HER OWN WORDS

"I was sitting under a tree on top of this hill, and a group of female muriqui had been feeding on myrtle berries and were resting in a nearby tree. I heard movement on the ground behind me and looked over, and crashing through the leaves is this male from another group. I think he didn't see me because when I turned around, he got startled, made an alarm call and ran to the nearest tree just a few meters away.

Four of my females rushed toward me in response to his alarm call. They were in a tree right in front of me, in full view. When they spotted the male, they stopped suddenly and huddled with one another. They looked at me, and they looked at him, and they looked at me, and they looked at him.

And they chased him away! He just took off down the hill, and they chased him through the canopy. Then they came back up in the tree right above me and started hugging each other, hanging down by their tails. A couple of them separated and put their arms down toward me.

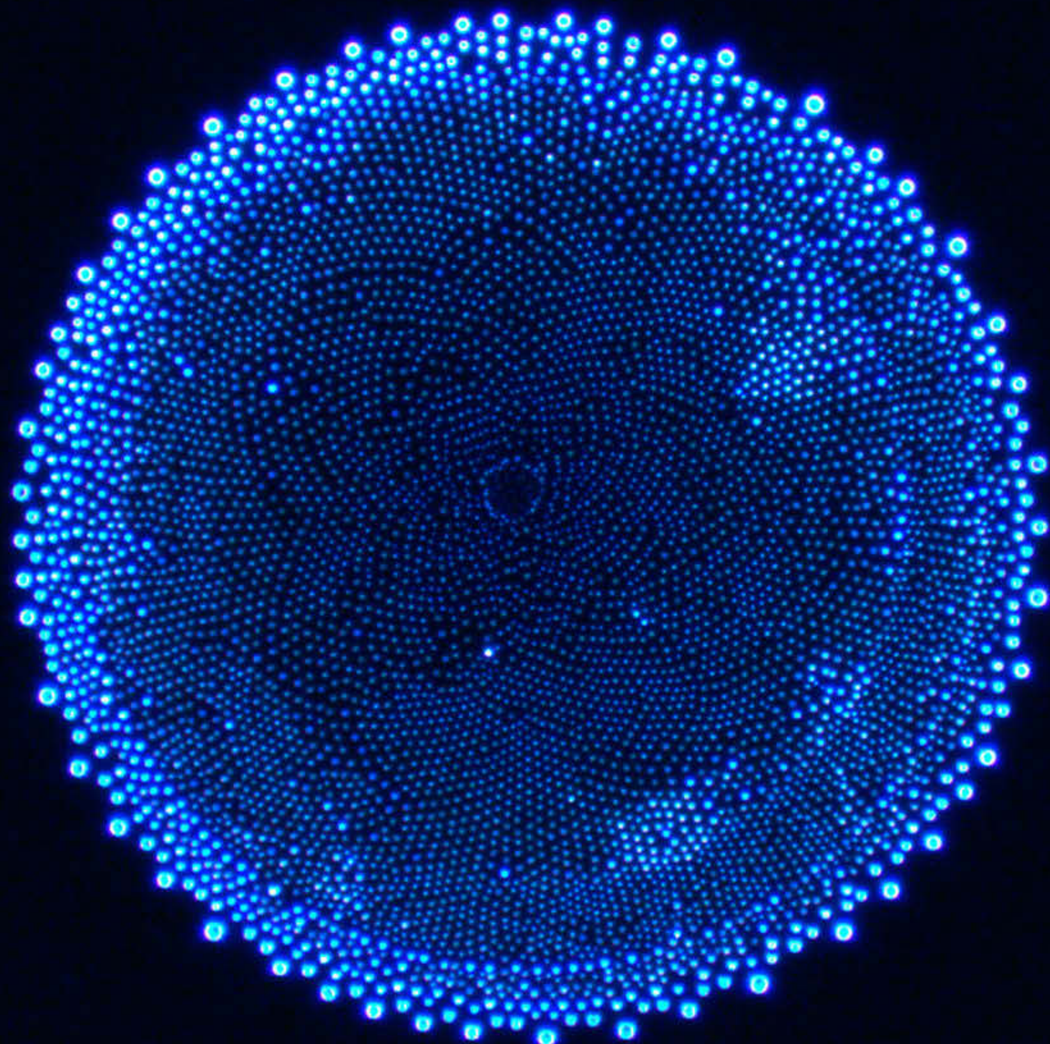
They were doing exactly what I'd seen them do before with each other: An animal in their group gets scared, or is threatened, and they hug each other in solidarity. And here they were, extending their arms to me.

It moved me to really caring about them as individuals in a way that has contributed to the perpetuation of this research. This little island of forest in the middle of nowhere supports these animals that are completely different from anything we know about.

These animals are so peaceful, so gentle and so nurturing. In a world full of wars, aggression, competition and violence, to have these animals that don't fight — it really gives me hope."

— AS TOLD TO ERIK NESS

TOP: CARLA B. POSSAMAI. BOTTOM: RUSSELL A. MITTERMEIER



## DRIP DRY

**This striking picture of drying water droplets is actually a mistake, says Devin Brown, a research engineer at Georgia Tech's Institute for Electronics and Nanotechnology. One day while he was etching microscopic patterns on a silicon chip with an electron beam, he noticed an accidental splatter of water only half a millimeter wide outside his target area. Intrigued, he decided to photograph it through an optical microscope. "It was just a defect at the edge of the sample that was interesting," says Brown, who was working on new nanofabrication techniques when he took the photo. The accidental image won grand prize in the 2013 Electron, Ion and Photon Beam Technology and Nanofabrication micrograph contest.**
— ERNIE MASTROIANNI

TOP: DEVIN BROWN/GEORGIA TECH INSTITUTE FOR ELECTRONICS AND NANOTECHNOLOGY. BOTTOM: ALEX WILD

## INBOX

### Mosquito Misstep?

*Several readers raised concerns in response to the May issue's Big Idea column about genetically engineering mosquitoes to resist carrying malaria and dengue fever — or to eliminate the species completely. Here's an example:*

Do we never learn? I'm a trained Fish and Wildlife technician and a retired park naturalist. Bats, amphibians and many other animals rely on mosquitoes as a food source, not to mention benefits we may not have even discovered yet. The food web would be badly affected by messing with this vitally important insect. Let's look at saner, better-thought-out solutions and not create a whole new set of problems. Perhaps developing more effective repellents and clothing for people to wear safely would be one possible venue to slow these deadly diseases.

***Laurie Eytel*** *Renfrew, PA*

***Author Jeff Wheelwright responds:*** *Whether we ought to be messing with Mother Nature is a common concern, and it's shared by the scientists who work on these projects. That's one reason why the first field trials of modified mosquitoes try only for local eradication around cities, leaving most of the wild population untouched. Down the road, if mosquitoes can be altered without killing them, merely blocking their capacity to spread disease, that might also allay concerns.*


June 2010 issue

# 'Insanity Virus' Research Advances

First human trials are underway.

**In 2010,** *Discover* reported on a theory that brain diseases such as multiple sclerosis (MS) and schizophrenia might have a common source — a virus. Researchers found mounting evidence that we carry this virus in our DNA, like the genes for left-handedness. What's more, infections such as influenza, picked up from our environment early in life, might be the trigger for these diseases.

The theory: Millions of years ago, an ancient human ancestor contracted a retrovirus that inserted its DNA into the host's reproductive germ cells, passing the viral DNA down the ancestral line. The virus, called human endogenous retrovirus W (HERV-W), codes for a protein that, when activated, sets off an inflammatory cascade in the brain that leads to symptoms. This theory is gaining traction among psychiatrists, especially as a potential explanation for schizophrenia, a disease once considered a result of bad parenting.

Since 2010, clinical trials have tried to target and neutralize that HERV-W-coded protein using monoclonal antibody therapy (MAT). Monoclonal antibodies are engineered to target specific receptors on infected cells, like inserting a key into a lock. Once the antibody binds, the immune system sees the cell as foreign and launches an attack.

In 2012, this approach passed FDA Phase I (human) trials as an MS treatment. Because of MAT's proven safety, HERV-W expert Hervé Perron, scientific director of GeNeuro in Switzerland, is looking to start Phase II trials for patients with schizophrenia. But Perron is emphatic: Although the research looks promising, especially for use in MS, a lot still needs to be done until we can see this as a general treatment for schizophrenia or MS.

— KATIE BO WILLIAMS

# Keep It Together

Astronomers learn what binds a potentially deadly space rock.

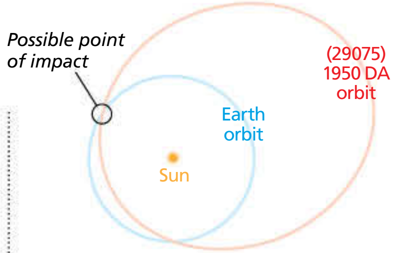
**Just a few million** kilometers away lurks a mysterious, and possibly deadly, asteroid called (29075) 1950 DA. Since the rock's discovery 65 years ago, scientists have learned the roughly mile-long body actually consists of a loose collection of smaller rocks, which they presumed were held together by their own gravity.

But in 2007, scientists discovered that 1950 DA also spins quickly, once every two hours — far too fast for gravity to hold it together. How could this pile of rubble not tear itself apart?

In August, physicists at the University of Tennessee announced that the force that holds 1950 DA together is the same force that allows the fine hair on a gecko's feet to stick to vertical surfaces: namely, weak electric attraction between individual molecules, called van der Waals' forces. Using data from NASA's Wide-field Infrared

**A loose collection of rocks, held together by van der Waals' forces, make up asteroid (29075) 1950 DA.**

Survey Explorer, the team created a computer model of 1950 DA. They found that the pieces of the asteroid are so small at the surface — 2 inches across, at most — that van der Waals' forces work with




**Asteroid (29075) 1950 DA might hit Earth in 2880, so the more we know about it, the better.**

gravity to secure the tiny pieces together.

There's a slim chance 1950 DA will hit Earth in 2880, and thanks to this finding, we'll know blasting the asteroid apart would be worse than useless: A strike might create multiple jumbles of rocks (held together with van der Waals' forces and gravity) heading our way. Luckily, there's plenty of time for scientists to dream up a different way to deflect the strange collection of rocks.

—SHANNON PALUS

LEFT: NASA/JPL-CALTECH. RIGHT: ALISON MACKEY/DISCOVER AFTER J. GIORGINI (JPL)

# The Wrong White Crystal

Although we've focused on salt, limiting added sugar could reduce high blood pressure and heart disease more effectively.


**Conventional wisdom:** Sodium consumption causes high blood pressure and heart disease, so we should eat less salt.

**Contrarian view:** Added sugars are more to blame for high blood pressure and heart disease, so we should reduce them instead of sodium.

High blood pressure, or hypertension, is the leading cause of America's No. 1 killer of both women and men: heart disease. Studies have shown that reducing sodium can help control blood pressure, and since the late 1970s, the government and physicians have preached skipping the salt to cut our heart disease risk.

But surprisingly, reducing just sodium isn't all that effective at dropping blood pressure. "Sodium intake is only one — and for most people not necessarily a large — factor in chronic hypertension," says Hillel Cohen, co-executive editor of the *American Journal of Hypertension* and a clinical epidemiology and population health professor at the Albert Einstein College of Medicine. Most clinical trials show that cutting out 1,000 milligrams of sodium from a diet, a relatively large amount, results in only a small drop in blood pressure on average, Cohen says.

That's partly because different people likely react to sodium in different ways. "There has long been consensus among hypertension specialists that some, but not all, people are 'salt sensitive,'" Cohen says. So really, relatively few of us see meaningful blood pressure benefits from cutting salt.

We may even be going a little too far with our low-salt approach. Currently, the USDA's Dietary Guidelines for Americans recommend consuming no more than 2,300 milligrams, or 1 teaspoon, of salt daily. The American Heart Association caps us at 1,500 milligrams daily. But a 2013 Institute of Medicine report found insufficient evidence to support restricting sodium consumption below 2,300 milligrams per day to prevent cardiovascular disease in the general population.

Instead, the focus should be on another white crystal. "When we think of heart disease and high blood pressure, the main dietary villain that we've been trained to think about is salt, when it's actually sugar," says James DiNicolantonio, a cardiovascular research scientist at St. Luke's Mid America Heart Institute in Missouri and associate editor at the journal *Open Heart*. DiNicolantonio recently co-wrote a review of studies, published in the journal, about the effects of salt and sugar on high blood pressure and cardiovascular disease.

Added sugar, such as the kind that's abundant in processed foods, isn't a necessary nutrient like sodium. DiNicolantonio's review points out that drinking sugar-sweetened beverages, one of the most popular added-sugar sources, ups blood pressure levels and is associated with an increased incidence of hypertension. More alarmingly, people who get at least 25 percent of their daily calories from added sugar — or 13 percent of the U.S. population — are almost three times as likely to die from cardiovascular disease than those who get just 10 percent of calories from the sweet stuff.

Cohen, who wasn't involved with the review, explains that sugar and hypertension are likely linked, in large part, by excess calorie consumption and weight gain. After all, being overweight is a risk factor for high blood pressure. (The more you weigh, the more blood your tissues need to keep up oxygen and nutrient levels. The increase in blood volume tends to put more pressure on your vascular walls.) DiNicolantonio adds that excess sugar causes fluid retention, which also drives up blood volume and pressure, far more than excess salt.

So instead of obsessing over the saltshaker, it's possible we'd improve our health more by cutting back on sweetened foods, with sugary drinks at the top of that list. — JENNIFER ABBASI

**DID YOU KNOW?** Apparently, some dogs see the water bowl as half-empty. Researchers at the University of Sydney found dogs' reward expectations varied widely by individual, suggesting some dogs are pessimists. The pessimistic pup may not be unhappy, though — just more cautious.

THIS PAGE: MAHATHIR MOHD YASIN/SHUTTERSTOCK. OPPOSITE: ERNIE MASTROIANNI/DISCOVER

# Ask Discover

Carbonaceous chondrites may have brought water to Earth.

**Q** Supernovas produce most of the heavy elements, but what about non-element molecules, like water and ammonia and many others we find naturally on Earth? And how did these molecules survive the incredible temperatures and impacts when the planet was forming?

*— Terry Guerrant, via e-mail*

**A** Most scientists believe that stable molecules like water and ammonia weren't originally produced on Earth. Instead, they arrived from space within the first 700 million years of Earth's existence. But how and when this happened still isn't clear.

When Earth formed about 4.6 billion years ago, water was already present in some form in the universe. It coalesced through gravitational forces just like how larger structures — such as rocks, crystals and Earth itself — were forming.

Some of that water was contained as ice in primitive meteorites called carbonaceous chondrites. In 2013 scientists compared the relative amounts of hydrogen and a hydrogen isotope present in Earth's water with levels present in the remnants of ice in these meteorites. Like a chemical fingerprint, the isotopic ratio between Earth's samples and the carbonaceous chondrites' samples matched. This find suggested meteorites that struck Earth during a period of heavy bombardment, between 3.8 billion and 4 billion years ago, likely introduced water. The arrival mechanism for other non-element molecules, like ammonia, is probably similar.

How did water "survive" the early heat? It didn't. It would've evaporated back into space until Earth cooled sufficiently. Exactly when it cooled enough to become water-friendly is still under debate. – KATIE BO WILLIAMS

Visit **DiscoverMagazine.com/Ask** for more answers. To submit a question, send an email to **Ask@DiscoverMagazine.com**

## DID YOU KNOW?

**Maybe you should ask how long your doctor's been working before you offer a handshake. A study from the American Psychological Association found that hospital workers' compliance with hand-washing standards decreased over the course of a typical 12-hour work shift. The effect was also cumulative: The longer the hours worked in the previous week, the worse the hand-washing hygiene, whereas taking longer breaks between shifts improved compliance to standards.**

# Tomorrow's Cancer Treatment?

Specially designed stem cells will target and eradicate tumors throughout the body.

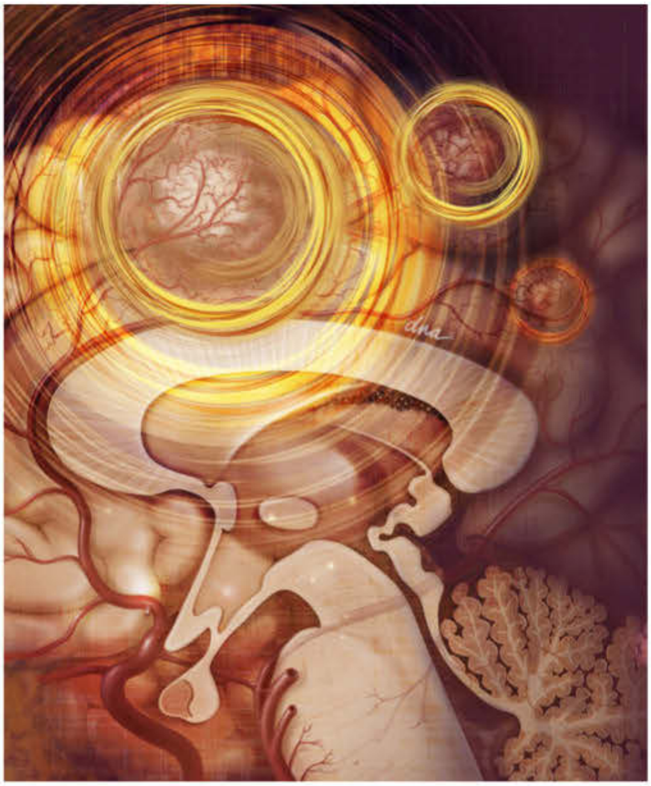
BY ELIE DOLGIN

One of the first things Doug Heil noticed was the gibberish on the screen. It was March 2014, and Heil was at his computer, filling out work orders for the construction company he runs in the San Gabriel Valley of Southern California. All of a sudden, he could no longer string the letters together to form a single word. Heil hurried to the nearest hospital, where scans revealed he had glioblastoma, the fastest-growing type of brain cancer. Doctors gave him 15 months to live.

Surgeons at the City of Hope Medical Center cut a tumor the size of a tennis ball out of the left side of Heil's brain. The symptoms quickly abated. Heil was back at work just two weeks later, and he even started riding his dirt bike again at the local motocross track. Yet within six months, despite continued radiation and chemotherapy, the cancer had grown again. Heil had two options: stick with a standard treatment with little chance of beating the tumor, or enroll in a new trial at City of Hope.

On Oct. 28, the 58-year-old Heil went back under the knife. Once again, surgeons removed as much of the tumor as possible, but this time they also injected tens of millions of neural stem cells and inserted a catheter deep into Heil's brain. On regular biweekly intervals thereafter, he could receive another infusion of the cells, each genetically engineered for tumor destruction.

Heil was the first patient ever to receive multiple doses of this new cancer therapy — one that, like all experimental medicines, carries risks of unknown side effects and treatment failure. "The thought of being No. 1 on the list didn't bother me," says Heil. "I'm fearless."



Tumors (circled areas above) naturally attract stem cells, so doctors decided to use those cells as delivery systems for cancer-fighting agents.

DNA ILLUSTRATIONS/SCIENCE SOURCE

## MISSILE DEFENSE

Stem cells are renowned for their regenerative capacity, able to grow into many different kinds of cells in the body. While still a controversial subject, many stem cells in clinical trials today don't require the deliberate destruction of an embryo but can be obtained from adult tissues. These cells are being tested widely as a way to repair tissue lost in diseases as varied as spinal cord injury, heart failure and diabetes. But many types of stem cells also have a unique ability to seek out cancer cells, making them potential agents of cell death as well.

Tumors release proteins that naturally attract stem cells (the reasons why remain unknown), so these cells can serve as biological delivery vehicles to cancer tissue, releasing therapeutic payloads directly at the site of malignancy. "It's sort of like having a heat-seeking missile," says Maciej Lesniak, a neurosurgeon at the University of Chicago. "And the question is, 'Which warhead do you put on top of it?'"

In Heil's case, the warhead was a special type of enzyme that converts a nontoxic medication known as a prodrug, taken separately and orally, into an active cell-killing agent. This helps ensure selective drug targeting only at the site of the tumor. Other research teams are loading stem cells directly with cancer-killing viruses and proteins. If the strategy works, it could provide a powerful new weapon against almost any kind of tumor in the body.

"I'm cautiously optimistic," says Jana Portnow, who's running the clinical trial at City of Hope and serves as Heil's doctor. "It has a lot of potential."

## STAY ON TARGET

In the City of Hope trial, participants like Heil receive 50 million to 150 million engineered stem cells every two weeks, followed each time by a seven-day course of the prodrug, called flucytosine. Prodrugs are pharmacologically inactive chemicals that the body can metabolize to produce a drug. In this case, our cells lack the enzyme necessary to activate flucytosine, but when it enters the brain and encounters the genetically modified stem cells, it becomes a cancer-destroying poison.

This approach carries some safety concerns. Because of the special ability of stem cells to self-renew and differentiate into other cell types, the cells could theoretically start replicating out of control and form tumors themselves. However, Portnow and her clinical team did not see any such problems in an earlier pilot trial in which they administered just a single dose of the engineered stem cells into the brains of 15 cancer patients.

That pilot study was designed only to confirm safety — and it did — but it also showed early signs that the therapy could work. "We have evidence that the stem cells did in fact convert the prodrug to an active chemotherapeutic agent in the brain," says Karen Aboody, the translational researcher at City of Hope who developed the therapy.

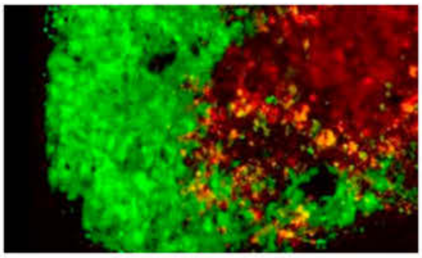
In Heil's trial — which enrolled its second and third participants this past spring — the City of Hope researchers are now directly testing whether more cells, given for longer, can actually halt tumor growth without causing any undue harm.

## A PLATFORM TECHNOLOGY

The treatment is promising enough that research teams around the world are developing similar stem cell therapies that can target and eradicate cancers of the prostate, lung, breast, skin and other tissues. In Germany, for example, the Munich-based biotech company apceth has already treated patients' gastrointestinal cancer with stem cells harvested from their own bone marrow and modified to convert a prodrug called ganciclovir. Among the first six patients treated to date, four responded favorably to the therapy.

Meanwhile, at the MD Anderson Cancer Center in Texas, Michael Andreeff and his colleagues are gearing up to launch their own stem cell trial for women with metastatic ovarian cancer. The bone marrow stem cells in this case come from a stock supply and are engineered to produce a protein that inhibits tumor growth called interferon-beta. Andreeff could treat the first patients as early as this summer. Trials of breast or melanoma cancer (treated with these same stem cells) could be next.

**The viruses replicate in the stem cells as they migrate to the site of the tumor.**



Tumor cells (green) under attack by virus-carrying stem cells (red).

KHALID SHAH/MGH

"This is really a platform technology — it can be adapted to almost any of the solid tumors," says Frank Marini, who worked with Andreeff before moving to the Wake Forest Institute for Regenerative Medicine in North Carolina.

Still, the need for stem cell-mediated delivery is arguably greatest in brain cancer because most standard drugs cannot easily penetrate the barrier that separates the blood (through which drugs typically enter the body) and the brain. With an estimated 190,000 people globally dying each year from tumors of the brain and nervous system, and no significant changes in patient survival in the past two decades, "we need to do something different," says Khalid Shah, a cancer biologist at Massachusetts General Hospital.

In one of his strategies, Shah is loading stem cells with cancer-slaying, or oncolytic, viruses. "The beauty of the oncolytic virus is that when the cell gets killed, it releases more virus, and that infects more cells," says Shah. "There's a chain reaction." The viruses replicate in the stem cells as they migrate to the site of the tumor. Viral agents then burst out of the stem cells, infecting the cancer tissue — but leaving healthy brain tissue alone. (In one common system, the virus is engineered with a gene deletion that prevents replication in healthy neurons.) The cycle of cell death then starts all over again. While Shah's work is promising, it's only been tested in mice so far.

Sadly for Heil, the prodrug-converting stem cells weren't enough. In February, after eight infusions of the new cell therapy, scans showed that his tumor had returned.

Heil is as pragmatic as he is fearless. "I knew I was going to die anyway, so I was willing to help for the betterment of medicine," he says. For him, "nothing has changed" because of the trial. But for medicine, the experience could help bring stem cell therapies one step closer to cancer patients everywhere.

"We learned a lot," says Portnow. "He clearly didn't have any bad immune responses to the stem cells, so that's encouraging." Maybe with other patients, the treatment will prove effective, too. D

***Elie Dolgin*** *is a science writer in Somerville, Mass.*

# Talking Heads

What happens when scientists try to eavesdrop on the inner voice?

BY CASSANDRA WILLYARD

ROY SCOTT/IKON IMAGES/CORBIS

Halfway into my first marathon, a nagging ache begins to seep from my feet into my ankles. "The wheels are falling off the bus," I yell as I pass my husband on the sidelines. I'm half-joking, but by the time I hit mile 20, the ache becomes a searing pain. Each time my sneakers strike the trail, the blisters on my toes threaten to rupture. I am in agony. The sound of Billy Joel blasting through my earphones isn't loud enough to drown out the inner voice that says, "You can't do this. You've failed." My jog slows to a trot, and soon, I'm hobbling.

After the race, I start to wonder whether it was my body or my mind that gave up first. Could I have kept running if the voice had shut up? And what is this voice, anyway? Where does it come from, and why do we have it?

In search of answers, I begin combing through the scientific literature. One man's name appears again and again: Lev Vygotsky, a Russian psychologist. He proposed in the 1930s that our inner voice evolves when we are still children. We first learn to use speech to communicate with others. Soon, we begin to speak to ourselves, too. We've all heard children talk to themselves as they build Lego battleships or whip up imaginary pancakes. Eventually, Vygotsky wrote, those private conversations begin to take place silently inside our heads.

Many people still subscribe to this theory, I discover, including Charles

**Try having a thought and documenting it at the same time, and you'll begin to understand the problem scientists are up against.**

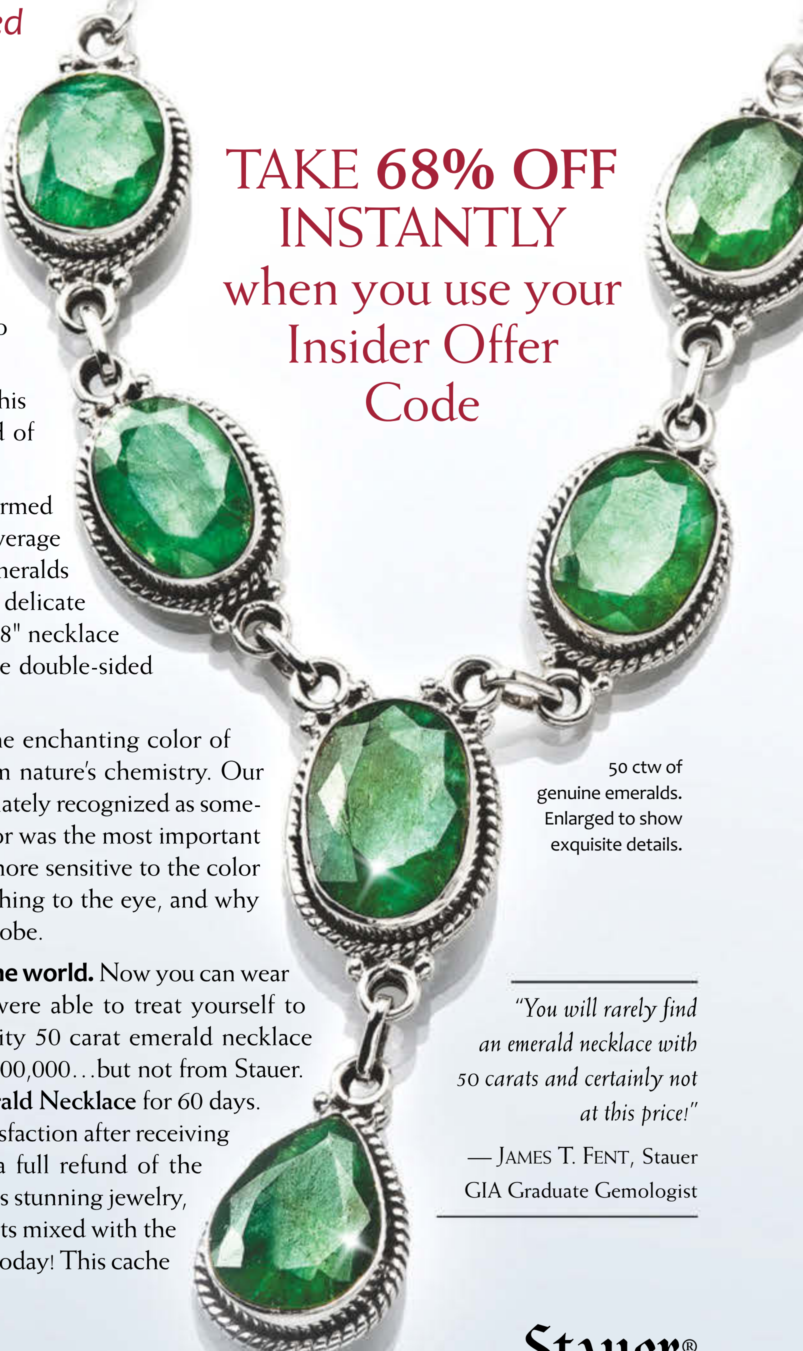
Fernyhough, a psychologist at Durham University in Britain who studies the relationship between inner speech and voice hearing. "Inner speech is just private speech that has been fully internalized," he tells me. "The stuff that you do in your head as you're running the marathon is basically a version of the stuff you used to do out loud as a kid."

Because this dialogue is internal, it's incredibly tricky to study. There are good reasons to think that, by attempting to observe this private experience, you invariably alter its content. Try having a thought and documenting it at the same time, and you'll begin to understand the problem scientists are up against. That's why even though scientists began wondering about the inner voice decades ago, few tried to rigorously study the phenomenon.

"They just thought it's something that cannot be explored by science," Fernyhough says. Even Vygotsky complained that "the area of inner speech is one of the most difficult to investigate." But in recent years, several researchers have begun to really listen to the voices inside our heads. And they now have a clearer picture of what the inner voice is — and what it isn't.

## BEEP, BEEP

To better understand my inner voice and its inclination toward self-doubt, I approach Russell Hurlburt, a psychologist at the University of Nevada in Las Vegas. For the past four decades, Hurlburt has tried to make sense of our common inner experience by cataloging hundreds of individual experiences. He gives his subjects beepers programmed to sound an alarm several times a day as they go about their lives. When his subjects get a beep, they make a detailed record of what was going on internally at that moment. Then, at the end of each day, Hurlburt sits down with the subjects and interviews them. The interviews are key,



he says, because people must be trained to capture their mental processes.

"We're going to try to tease apart your actual experience of your inner voice from your pre-suppositions about your inner voice," he explains. "If there are words in your inner experience, I would like to know exactly what they are."

Often, Hurlbert finds, there aren't words. Some thoughts take the form of pictures, sensations, or have no form at all. In fact, Hurlburt's research suggests that inner speaking happens only in about a quarter of his patients' experiences, and that its frequency varies widely from person to person. Some people don't ever talk to themselves, while others seem to chatter nearly constantly. One of Hurlburt's subjects reported that she was engaged in inner speech 94 percent of the times her beeper sounded.

Curious to hear Hurlburt's thoughts on my inner critic, I begin to tell him about my marathon experience, but he stops me. "I have found on many occasions, maybe even most occasions, that people are mistaken about their own inner experience," he says. That's because people tend to assess their inner voices by reflecting on events after they occur, a process prone to bias. "I doubt that you have a really good reason to believe that your inner voice is as negative as you say it is," Hurlburt says.

Could he be right? To find out, I try a slightly modified version of Hurlburt's test. I dutifully record my inner voice for five days, but instead of carrying a beeper, I ask my husband to program my phone to automatically send me six text prompts over the course of a day. When I receive a message, I jot down what's going on. Instead of meeting with Hurlburt daily, I talk about my experiences with my husband.

The experiment doesn't provide any earth-shattering insight into my psyche, but it does confirm Hurlburt's

**I've always assumed my inner voice babbles pretty much constantly, but often when the beep sounds, there are no words at all.**

suspicions. Not once does the prompt capture my familiar inner pessimist. Instead of criticizing, the voice wonders if my adult-size head would fit into a child-size stocking cap; it pines for a time when we weren't all glued to our cell phones; and it mentally composes an email to a contractor. I've always assumed my inner voice babbles pretty much constantly, but often when the beep sounds, there are no words at all.

## BEHAVE YOURSELF

So why does this inner voice choose to pipe up on some occasions and remain mute on others? Dolores Albarracin, a psychologist at the University of Illinois at Urbana-Champaign, says it typically appears "when you're really worried, or really anxious." Albarracin and her colleagues found that negative situations and internal struggles tend to elicit a "splitting of the mind" that transforms the inner voice into something of a surrogate parent. Rather than saying, "I can do it," your inner voice might say, "You can do it." (Or, in my case, "You can't do it.")

Inner speech also seems to help people perform certain kinds of cognitive tasks. Fernyhough and his colleagues asked children to play a game that involved placing colored disks on sticks to create a pattern while simultaneously repeating the word "Monday" — an activity designed to suppress the inner voice — or tapping their foot, which doesn't affect inner speech. The Monday repeaters performed worse than the toe tappers.

The inner voice can be a harsh critic, as I discovered during the marathon. But James Hardy, a sports psychologist at Bangor University in Wales, says that typically, in the realm of sports at least, negative self-talk doesn't necessarily have much of a detrimental impact on performance. In fact, a little negativity can sometimes "act as a bit of a kick in the backside," Hardy says. Imagine you're playing tennis, and you miss an easy shot. A negative inner tirade might motivate you to do better next time.

A year after my disastrous debut, I ran a second marathon. Rather than allowing a negative voice to derail my race, I selected a positive mantra, a phrase that might help motivate me. When my feet began to ache, I repeated these words: "You've trained for this." It's possible this phrase simply distracted me, or that repeating it blocked the negative words I might have said. But it's also possible that these encouraging words helped me push through the pain. Either way, this time, I finished the race with a smile. D

***Cassandra Willyard** is a freelance science writer based in Madison, Wis.*

Subscribers, learn to listen to your own inner voice with our guide at **DiscoverMagazine.com/InnerVoice**

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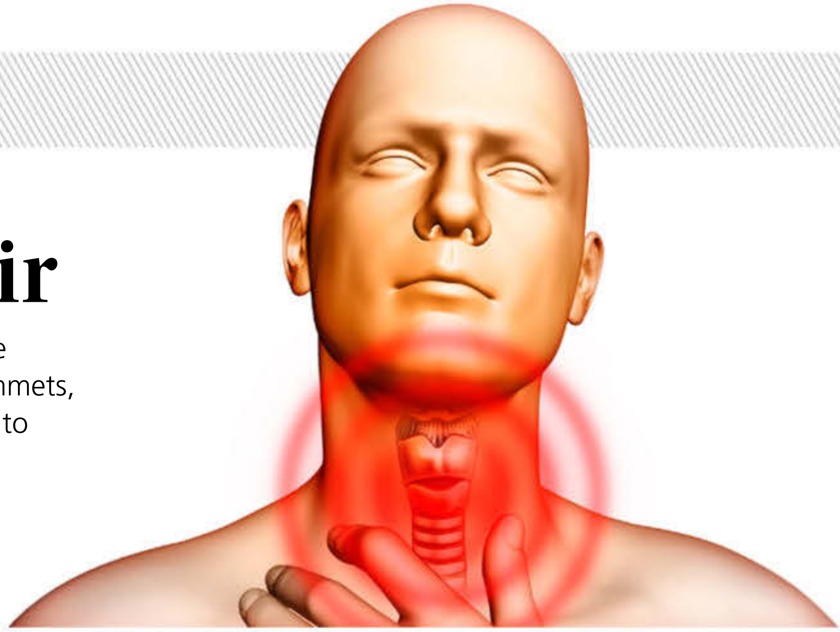


# Clear the Air

A man clutches at his throat, unable to breathe. As his oxygen level plummets, the race is on to get a tube safely into his trachea in a matter of seconds.

BY **TONY DAJER**

The ambulance-bay doors hissed apart. A man staggered in. Face contorted in panic, hand on his throat, he croaked, "I can't breathe!"

Not true, I thought dimly. Here you are, shouting at us.

Victoria, the triage nurse, hustled him into the trauma slot. More nurses swarmed.

"You'll be OK," I said.

Eyes wide, he dropped his hand. He was thin and sinewy, so I expected him to sport a prominent Adam's apple. Instead, he uncovered a sickly blue mound. I reached to feel it, but he jerked back.

"Can't breathe!" he rasped. His hands clenched my forearms in a wrestler's grip.

I ordered nebulized epinephrine, thinking it would shrink swollen throat tissues. The trauma team, three residents and their attending physician, barreled in. The friend who drove him to the ER appeared.

"What happened?" four of us shouted.

"Second base. Line drive got him right here," he said, chopping at his own throat.

The pulse oximeter lit up: 78. Pulse oximetry measures the percentage of arterial hemoglobin carrying oxygen. Normal is 96 to 100 percent. But 78? I'd never seen a patient that low talk, much less walk.

I gawked at the screen, willing it higher. The oximeter's finger probe often picks up better after a few seconds. This one dropped. I grabbed the mask with epinephrine, cranked the oxygen and jammed it on his face. Flailing now, he shoved me away.

"Hold this on," I said.

His face turned dusky. The pulse ox lurched below 70 percent.

Grace, the trauma chief, sidled up. "No choice, really," she said in a this-ship-is-going-down tone. By then I'd grabbed a laryngoscope to see into his throat and an endotracheal tube to insert down his windpipe. I offered them to Grace — she was the trauma chief, and this was trauma. She lifted her chin: "Go ahead."

> **"Can't breathe!" he rasped. His hands clenched my forearms in a wrestler's grip.**

In a blur, multiple hands grabbed swinging arms and legs to center our patient on the stretcher. A nurse pushed a paralytic drug and a sedative into the IV line. The surgery residents swabbed his neck with iodine solution, ready to cut a hole in his neck if my intubation attempt failed.

Secure the airway — emergency medicine's holy grail. The goal: get a tube in the trachea to breathe for a patient who can't get oxygen in or carbon dioxide out, or both. The method: slide the curved steel blade of a laryngoscope into the mouth, push the tongue aside, then slip a plastic endotracheal tube — usually stiffened by an internal metal stylet — around the base of the tongue, under the epiglottis (the petal-like flap that covers the trachea when you swallow), away from the yawning esophagus below, through the narrow tracheal cartilage, between the vocal cords and into the windpipe. In inert, frail 90-year-olds, this is pretty easy; in thrashing, suffocating baseball players with smashed larynxes, less so.

Off oxygen, brain cells begin to die in four minutes. If that happens, it's your fault because good ER docs can always secure the airway. But we do sometimes fail; studies say about 1 percent of the time. The videos of tubes not going in — of rising panic as doctors jam and shove laryngoscopes in, of blood and vomit filling the throat — make for rapt audiences among young trainees.

Clever gadgets and better training help to head off that nightmare. Fiber-optic laryngoscopes give you a tip's-eye view to better navigate the throat's curves and narrows; form-fitted airway devices can go into the mouth to block the esophagus and deliver oxygen to the trachea; simulation dummies — computer-enhanced and lifelike — pop up everywhere; and newer paralytics and sedatives can take a patient down in less than a minute. (It's almost always better to intubate an unconscious, paralyzed patient than an awake, fighting one.)

ANDREA DANTI/SHUTTERSTOCK

But nothing's perfect. Rigid stylets inside fiber-optic-guided tubes can pierce tracheas; medications can drop blood pressure. Sometimes there is too much bleeding or no time or massive swelling, and you just miss.

The last resort is to cut into the neck and pierce the trachea ("cut to air," in the trade) and work a tube in — a bloody, risky proposition. Which is exactly what the surgeons were ready to do if I failed.

### IN SEARCH OF BREATH

I had one shot. As our patient went flaccid, two thoughts flew through my head. The first, how I would sound on the witness stand justifying time wasted on the nebulized epinephrine as brain cells died. The second, the well-recognized possibility that by manhandling a fractured larynx, I would disrupt the anatomy beyond rescue.

There was no more time. I pulled the mandible down with my right hand, hefted the laryngoscope handle with my left and slid the smooth, silver blade along the pebbly curve of the tongue.

Grace planted herself at my elbow. "Just look for cords," she said softly.

The top of the epiglottis came into view, drooping like a rose petal. A pool of yellow fluid blocked my view.

"Suction!"

I jammed the suction catheter in. Nothing.

"Here," Grace said, relieving me of the endotracheal tube. I'd been gripping both tubes together. Now I could suction.

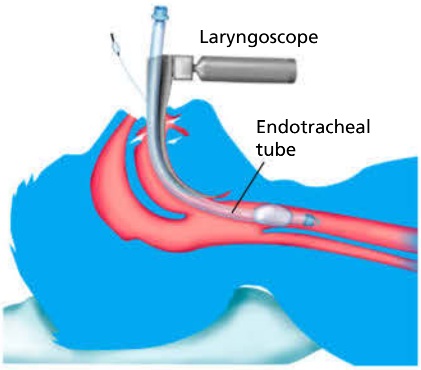
"Find the cords," she repeated.

Lifting the tongue, I spied the vallecula, the dip between tongue and epiglottis, and gingerly pushed the blade tip against it. The rose petal popped up to reveal — deep within their fortress of cartilage — the vocal cords.

"I see them," I said to my spotter.

Angry red lines — fractures? — crisscrossed the cartilage walls. To my relief, there was a gap between the cords. Blows to the neck can trigger cord spasm, effectively corking the airway. Paralytics are supposed to overcome that, but between spasm and disrupted anatomy, it wasn't safe to assume anything.

"Just go for cords," Grace whispered again, trading me suction catheter for endotracheal tube, which had a deflated balloon at its tip. Grabbing the tube at midcurve, I aimed for the dusky gap between the two shiny white cords, held my breath, then slowly — they always say go slow, or you'll bounce off tracheal cartilage into the esophagus — advanced to the opening and tried to jimmy the tube in. The deflated balloon around the tip snagged on the right cord.




"Jesus," I hissed. A gentle turn freed it. With a subtle give, the tube slipped through and home.

I straightened up. "In. I think."

The respiratory therapist pulled out my stylet, inflated the tip balloon through its small port at the top, attached an Ambu bag to the open mouth of the endotracheal tube and pushed in liters of oxygen. The carbon dioxide detector pulsed blue to yellow — the patient was breathing.

Stethoscope on chest, Grace announced, "Breath sounds equal."

A dozen furrowed brows relaxed.

A grinning, iodine-splattered resident walked over.

"Good tube."

The oxygen level flashed 70 percent, bounced to 75 percent, then surged to 98. But how was the brain?

"The meds are about to wear off," Grace said. "Snow him with fentanyl and propofol?"

"Sounds good," I agreed.

Red-hot needles under fingernails rank a distant second to waking up with a plastic tube down your windpipe. Fentanyl dampens pain; propofol sedates.

Grace and I manned the foot of the bed. Succinylcholine paralyzes up to about eight minutes. Our patient lay still. The ventilator purred. People bustled. Time was up. C'mon, move.

A nurse read off a lab slip, "Lactate 10.4."

My chest contracted. A measure of anaerobic metabolism, the lactate level reflects how oxygen-deprived the body has been. Septic, hypotensive patients are very sick when lactates top 4.

"He was running on fumes," Grace marveled.

### REGAINING CONTROL

It came all at once. The head began to rock, hands and feet twitched, then we had a bucking bronco. Instead of high-fiving Grace, I shouted, "Hold him! He's going to pull the tube!"

A dozen hands pinned him down. Eyes wild, he strained to yank the plastic tube gagging him.

"Let's double the meds," Grace urged.

Once the stronger sedation hit, the surgeons took him to CT scan. It showed a badly fractured larynx. He would likely need surgery, and he faced possible complications, like tracheal narrowing.

But for now, brain and airway were secure. D

*__Tony Dajer__ is director of the emergency department at New York-Presbyterian/Lower Manhattan Hospital. The cases described in Vital Signs are real, but names and certain details have been changed.*

BSIP/SCIENCE SOURCE

# PEELING BACK A CITY'S LAYERS

Underground transit projects offer archaeologists rare opportunities to dig into historic urban centers — but with the clock ticking.

BY **JENNIFER HATTAM**

The future reveals the past: A subway expansion project in Turkey unearths a lost port and the largest known collection of Byzantine shipwrecks.

THIS PAGE: STEFANO DAL POZZOLO/CONTRASTO/REDUX. OPPOSITE: ISTANBUL UNIVERSITY YENIKAPI SHIPWRECKS PROJECT ARCHIVE

Ufuk Kocabaş

**As a child growing up in Istanbul in the late 1970s,** Ufuk Kocabaş spent his summers swimming, snorkeling and eventually diving around nearby Marmara Island, where his grandfather and other forebears plied the sea as sailors. At age 14, he stumbled upon his first shipwreck, littered with pieces of amphora — an ancient type of storage and transport container — and got an early lesson in proper archaeological practice.

"I took some amphora fragments [from the ship] to my sister who was studying at university," recalls Kocabaş, now head of the Istanbul University Conservation Department. "She told me I shouldn't have taken them from the site, that I should have left them where they were. At the time, I thought this was stupid. It's my amphora!"

After chiding him, Kocabaş's sister helped him identify the type of amphora he found. It dated to the seventh century, and they passed the information they'd ascertained about the shipwreck to a museum. "It was an amazing experience," Kocabaş says. "I started to read about shipwrecks then, and haven't stopped since."

There would be plenty more amphorae and sunken vessels in Kocabaş's future. In 2005, shortly after receiving his doctorate in ancient history, he was tapped to help lead an urban archaeological excavation in his home city. The dig has revealed perhaps the world's largest collection of Byzantine shipwrecks, along with rare burial structures, the bones of dozens of animal species and thousands of prehistoric human footprints. All told, 35,000 artifacts dating as far back as the Neolithic period — from ceramics to coins, combs to cooking utensils — have been uncovered, providing new insights into daily life, trading routes and the age of the city itself.

The thought of such riches being found underfoot is hard to imagine while crossing the broad expanse of concrete that now leads to the Yenikapı subway station in central Istanbul. About a third of a mile from the sea today, the unshaded spot is scorching in summer and surrounded by construction cranes and boxy low-rise apartment blocks cheaply built in the 1980s. But from the fourth to the 11th century, it was a flourishing commercial and military harbor, the largest of the early Byzantine period. Trading ships from as far away as Crimea, North Africa and the Balkans pulled into port carrying wine, ivory, leather, ceramics, grain, construction materials, even exotic animals, from one distant end of the empire to another.

"The existence of the Port of Theodosius was known from written sources — from the writings of historians and voyagers — but we had no idea about its exact location or dimensions," Kocabaş explains while sitting in his lab, a nondescript warehouse near the Yenikapı dig site.

The port's whereabouts remained a mystery until work began in 2004 on a metro extension, including the new Yenikapı station, meant to ease congestion in a rapidly growing city infamous for its traffic jams. Instead of driving across one of two often-clogged bridges from the heavily residential Asian side of the city to the commercial centers of the European side, Istanbul commuters would be able to take the Marmaray rail tunnel under the waters of the Bosporus Strait. In a nod to the long history of the area around Yenikapı, a team from the Istanbul Archaeological Museums was brought in to conduct what was expected to be a short "salvage excavation" — a standard quick survey of a site about to be developed — before the station construction began.

As with most other such projects, the transit tunnels themselves run too deep below ground to disrupt any archaeological remnants, which are usually found when tunneling to build station entrances and other ground-level access points. The Yenikapı station sits 65 feet below the surface, while the oldest remains at the site, dating from the Neolithic period, were found more than 20 feet below the current sea level. The shipwrecks were unearthed at depths between 2 and 17 feet.

"A former classmate of mine who was working at the museum called me after they began finding the first pieces of a wreck," says Kocabaş, describing his initial visit to the site in 2005. "There was a piece of the wooden hull, some amphorae, pieces of an iron anchor, even lengths of rope."

The team had found the long-lost port of Theodosius.

"They were thinking they would just find one or two shipwrecks, but I told them they would find more than 25 because the city and harbor were so important," says Kocabaş. In the end,

OPPOSITE, BOTTOM LEFT: STEFANO DAL POZZOLO/CONTRASTO/REDUX. ALL OTHERS: ISTANBUL UNIVERSITY YENIKAPI SHIPWRECKS PROJECT ARCHIVE

Temporary sheds provide some shelter at the Yenikapı excavation site as the team documents timbers from 37 ships recovered from a lost Byzantine port.

An artist reconstruction shows how some of the Yenikapı vessels might have looked when they plied the Eastern Mediterranean and Bosporus Strait.

Each fragile, waterlogged fragment of the excavated ships was cleaned, photographed and documented, then injected with protective chemicals to prevent cracking or further damage.

Each shipwreck was documented *in situ* (above) using a method called total station mapping, similar to how surveyors create precise maps. While the ships captured most of the media attention, the Yenikapı site also yielded thousands of pottery shards that had to be sorted and documented (left).

37 wrecks were uncovered, including the first Byzantine galleys — slim, long warships — ever excavated, cargo-laden trading vessels and small sailing boats for local travel. All were remarkably well preserved below layers of silt deposited by a river that once ran through the area.

The site's importance was undeniable, but the clock was ticking on the massive multibillion-dollar Marmaray-Metro infrastructure project. Kocabaş and the other archaeologists had to assemble large teams to work long hours on the 625,000-square-foot site — an area larger than 10 football fields. The conditions were often difficult. Water had to be pumped out of the dig site for three hours early each morning before the teams could get to work, and an atomized spray system misted the wooden artifacts with water 24 hours a day so they wouldn't dry out and crack apart, suffering irreversible damage.

"Normally, you spend two months in the summer on a dig, then go back to your university and work on your objects and drawings. We were working in the mud year round, from 8 a.m. up to midnight sometimes, with the engineers waiting and sometimes getting angry," Kocabaş says. "We froze in the winter and sweltered in the summer. Three times, the city's sewer system overflowed into the dig trench after a big rain, and we had to pump it clear again. You never want to see that."

Describing the urban dig site as very "dynamic," Kocabaş says his early educational background in mechanical engineering, his father's profession, came in handy for devising new apparatuses to lift out parts of the ancient ships as they were uncovered. "We couldn't use mechanical tools in the excavation area because there were so many artifacts. Everything had to be moved by hand, but the wood was so soft, you couldn't even touch it," he says, showing photos of the L-shaped brackets and Styrofoam supports he designed so the workers could move the waterlogged vessels without damaging them. On the high-tech side, the team employed a total station device — a tripod-mounted cameralike instrument used by surveyors and engineers to

measure distance and angles. It captured up to 30,000 digital reference points on each *in situ* shipwreck to be assembled later into large-scale 3-D images.

Excavations were completed before the subway station's grand opening in fall 2013, but work to document and analyze the finds continues under Kocabaş's supervision at the Yenikapı Shipwrecks Project lab. Wooden timbers from the sunken ships are kept submerged in narrow rectangular tanks measuring some 10 to 30 feet long and housed inside the warehouse as well as in an adjacent lot. The timbers stay there, protected by the water until a lab tech is able to clean, photograph and digitally measure them, noting the size, shape and placement of every nail, tool mark or glob of pitch. Pieces ready for storage are impregnated with polyethylene glycol or melamine resin to prevent cracking. Smaller pieces are then dried in an oven while larger ones go into a 2.5-meter-long freeze-dryer/ condenser that resembles an MRI machine and is housed in its own trailer on the lab grounds.

"A vacuum moves all the water from the wood to the condenser section, where it quickly turns to vapor to keep the wood from cracking under the high tension," Kocabaş explains, proudly noting that the $80,000 device is the first of its kind used in Turkey. Similar equipment was used to preserve the largest Viking warship ever found after it was excavated from the banks of Denmark's Roskilde fjord. "Texas A&M University is the birthplace of nautical archaeology, but even they didn't have one like this when we got ours!"

The archaeologist smiled just as broadly, if perhaps a bit more mischievously, when pointing out his two secret weapons to keep the timbers still in the tanks from being damaged by bacteria, fungi or insect larvae. "That's Guardian, and that's Death Angel," he says, gesturing to two tiny fish swimming around one of the vats. "I took my son's goldfish when he was away at our summer house and told him they had to be put to work. They clean everything."

More than 10 years after the Yenikapı dig began, much remains to be done before the full significance of the finds is understood. "Each vessel will be a doctoral thesis in itself," Kocabaş says, adding, "I am very happy with the excavation result, but will only get a good night's sleep when we've exhibited the ships." City officials recently selected designs for a museum, or "arkeopark," to house the remains, but no timetable for such a project has yet been announced.

Mindful of both the historical significance of the dig and its impact on a high-profile urban transit project, Kocabaş has taken pains throughout the excavation to make it unusually accessible to the public, giving hundreds of lectures and welcoming visitors to the dig site and lab. Despite the added responsibilities and challenges, he recognizes that working on a transportation-linked excavation also provides opportunities archaeologists might not otherwise enjoy.

"We know there are Byzantine palaces all around [this part of Istanbul], but it's not easy to excavate a historic, heavily populated area like this," he says. "If it hadn't been for the construction of these subway tunnels, we would have kept walking on top of the shipwrecks without any knowledge of them."

# ISTANBUL
## A MUCH OLDER SETTLEMENT

Crates full of finds dating back more than 8,000 years suggest the archaeological wealth of Istanbul's Yenikapı site, seen in background.


Archaeologists digging below Istanbul's Yenikapı neighborhood uncovered more than a rich hoard of Byzantine shipwrecks. They also turned up evidence that the great city's history is even older than previously thought — by nearly 6,000 years.

"Before the excavation, we believed that Byzantium [the precursor to Istanbul] had been established in the seventh century B.C. by Greek colonists," says archaeologist Ufuk Kocabaş. "But then under the [Byzantine] harbor, we found Neolithic remains, which was very surprising. Now we understand that this city's history goes back to the Neolithic Age."

Human remains found in the earlier layers are still undergoing analysis. But funerary urns, wooden burial structures and the remains of buildings found below the Port of Theodosius date back around 8,500 years, according to the Istanbul Archaeological Museums, which supervised the Yenikapı excavations. The most heralded finds at the site provide insight into Byzantine shipbuilding techniques and trade routes. But thousands of other discoveries are revealing new details about animal populations of the time and their use by humans, as well as the Neolithic-era movement of people through Anatolia and Thrace in Europe, Kocabaş says: "There are many phases to this excavation. We'll be studying [the results] for years."

CLAUDIA WIENS. MAP BY JAY SMITH

# RIO DE JANEIRO
## GARBAGE IN, TREASURE OUT


**Excavations beneath Rio de Janeiro's Leopoldina neighborhood (above) revealed a treasure trove of trash discarded by aristocrats between the 17th and 19th centuries. Artifacts include what researchers believe is a ceramic spittoon (right) currently being reconstructed.**

**Archaeologist Cláudio Prado de Mello (above) cleans one of more than 200,000 artifacts, including a toothbrush that may have belonged to a royal (right).**

FROM TOP: LINE 4 SUBWAY/FVD STUDIOS (2); SILVIA IZQUIERDO/ASSOCIATED PRESS/CORBIS; PILAR OLIVARES/REUTERS/CORBIS; LINE 4 SUBWAY/FVD STUDIOS. MAP BY JAY SMITH

Excavations in Rio de Janeiro being carried out since 2012 as part of construction of a new subway line are revealing new details about the daily lives of the former Brazilian aristocracy — through their garbage.

The treasure trove of 17th- to 19th-century trash has come to light as part of work on a metro extension that will link parts of Rio de Janeiro's greater metro area with Barra da Tijuca, the main site of the 2016 Olympic Games.

**A white porcelain lid found at the site is emblazoned, "To the Queen of Portugal Maria of Saboia."**

"The royal palace was about 1 kilometer away [from the Subway Line 4 dig site], and our research in the archives showed that the area had been a place for discarded trash, so we suspected that we had a big discovery to make," says Cláudio Prado de Mello, director-president of the Institute of Historical and Archaeological Research of Rio de Janeiro. He has been leading the excavations in the Leopoldina neighborhood. "But when we began to remove the initial layers of the soil, we started to find thousands and thousands of objects from the imperial and colonial period," he says.

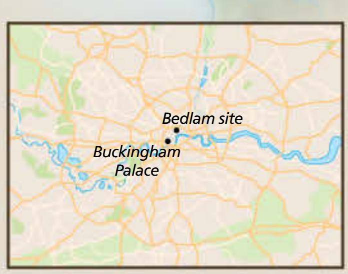
The 200,000-plus artifacts uncovered at the Leopoldina site so far include stoneware and glass bottles, some still filled with liquid; household ceramics; pipes; coins; remains of a leather shoe; and 15 bone and ivory toothbrushes, one inscribed in French with the words "His Majesty, the Emperor of Brazil." It is believed to have belonged to Dom Pedro II — the country's last monarch, ousted in a coup in 1889 — or another member of the royal family.

"Usually what is documented by writers about a state administration are the historical moments, not the daily life of the aristocracy," Prado de Mello says. "Now we have the opportunity to find a part of the past that is normally forgotten."

# LONDON
## BEDLAM BENEATH THE STREETS

Unearthed in March during London's multibillion-dollar Crossrail project, a skeleton from the centuries-old Bedlam burial grounds waits to be cataloged for further study.

JUSTIN TALLIS/AFP/GETTY IMAGES; MAP BY JAY SMITH


Crossrail, the $22.5 billion railway expansion that spans more than 60 miles, much of it through London's center, has unearthed finds dating back nearly 70,000 years. But it was in March that archaeologists began excavating the project's crown jewels — all 3,000 of them, give or take.

The thousands of skeletons originally interred from the mid-16th through 18th centuries at the Bedlam burial ground are expected to provide researchers with unparalleled information about a formative time for London that included the English Civil Wars, Restoration, the last major plague outbreak and The Great London Fire of 1666.

"It's unique in London's history," says Jay Carver, the lead project archaeologist for Crossrail. "It covers a period not represented in other finds on this scale."

The Bedlam site will give researchers a glimpse into the lives of ordinary Londoners as the city transformed into a modern capital. But the team also hopes to uncover one or more of the famous figures believed buried there, including John Lilburne, who ran afoul of the Crown in the

mid-17th century because of his progressive ideas about human rights.

"We don't know if it will be possible to find him because many of the burials were anonymous, and there are about eight bodies per cubic meter — that is extremely dense," says Carver. He added that his team is conducting the Bedlam excavations and research at an accelerated pace and plans to publish an open-access report by the end of 2016.

Layers beneath the Bedlam burial grounds include a Roman-era road and marshlands. Evidence of earlier wetlands is a common find in Crossrail digs — the Londoners of long ago traversed a much more watery world. Two wooden stakes found during excavations in east London, for example, are thought to have been part of a timber pathway used by hunters across the wetlands that covered the area 3,500 years ago.

Excavations for the new subway lines have also revealed a set of rudimentary ice skates dating back to Saxon or even Roman times: Cow bones were smoothed flat so they could be strapped to the feet to cross the frozen marshes of what is now central London.

"People previously had no idea about the depth of history in these places where they're living," says Carver. Members of his team spend much of their time consulting historical records, borehole logs and other data to model what might be underfoot so they can dig as quickly and accurately as possible and keep the infrastructure work moving ahead smoothly.

All their advance research led to what Carver describes as a "needle in a haystack" find in 2011 in west London: a buried channel dating back 68,000 years, full of bones of the prehistoric reindeer, bison and other animals that had the run of the place during the Pleistocene period.

"Revealing these really ancient landscapes is always extraordinary," says Carver. "It's London before London."

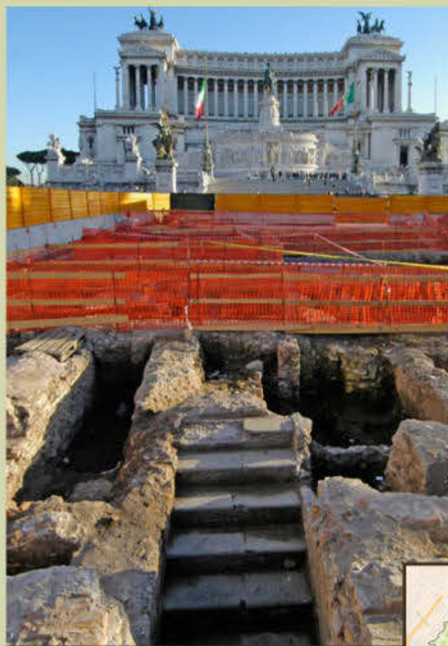

**In March 2015, archaeologists led excavations of the Bedlam burial grounds in central London. The site was found during construction of a ticket hall next to the Liverpool Street Station, part of a big Crossrail expansion.**

The Bedlam site was a challenge to excavate because of the high density of bodies buried there: up to eight skeletons per cubic meter.

A mother and child were among the thousands of skeletons found at Bedlam, London's first municipal burial ground.

Each skeleton unearthed at the Bedlam site last spring was carefully documented, bagged and removed for further study.

CLOCKWISE FROM OPPOSITE: C CROSSRAIL LTD (2); MIMMO FRASSINETI/AGF; SUZANNE PLUNKETT/REUTERS/CORBIS; CROSSRAIL. MAP BY JAY SMITH



In the shadow of Rome's Piazza Venezia, subway construction workers found a cultural center that's nearly 2,000 years old.


# ROME
## FIRST-CENTURY CULTURE

When digging underneath Rome, it would be a surprise *not* to run across an ancient artifact or two. But excavation teams were still amazed by what they found below the heavily trafficked Piazza Venezia while building the Metro C line subway extension between 2007 and 2011. Archaeologists uncovered a two-story cultural center built during the reign of Emperor Hadrian nearly two millennia ago.

The partially preserved building's three large halls were decorated with colorfully painted marble and used for cultural events, oratory and poetry contests.

"Probably the most impressive single piece uncovered there is a section of seating with a marble balustrade, where people would watch the performances and listen to declamations," says Darius Arya, a Rome-based archaeologist and executive director of the American Institute for Roman Culture. "The excavations show the structure's whole life cycle — the damage done by earthquakes, the pillaging, the medieval structures built on top using parts of the original building."

Another standout find during the digs — the "biggest archaeological investigation ever conducted on Roman soil," according to the Rome Metro company — has been the discovery, announced in late 2014, of a large working farm close to the city's ancient center. "You think of first-century Rome as being crowded and urban, but there was food being produced locally," Arya says. "An abundant supply of peach pits was found at that site, so we know there were peach trees on that farm."

The ongoing archaeology work for Metro C has also revealed the remains — copper slag and ingots, as well as the holes dug for small furnaces — of a sixth-century metallurgical workshop, the largest known in Rome from its time period. D

***Jennifer Hattam*** *is based in Istanbul. This is her first feature story for* Discover.

# SUPER EARTHS

## They're big. They're weird. They're everywhere.

Worlds a few times larger than ours might be the best bet for finding another habitable planet.

BY **ADAM HADHAZY**

MARK A. GARLICK/MARKGARLICK.COM

The sun is just rising on our search for super-Earth planets beyond our solar system.

# JUST 23 YEARS AGO, OUR SOLAR SYSTEM'S PLANETS WERE ALONE IN THE UNIVERSE.

Scientists naively presumed if we ever did discover planets around other stars, these worlds would look, well, *familiar*. "We imagined we were going to find other planetary systems in our own image," says Andrew Howard, an astronomer at the University of Hawaii.

Boy, were we wrong. Among the 1,900-and-counting confirmed alien planets found so far, we've seen everything from bizarro, jumbo versions of Jupiter in scorchingly tight orbits to exoplanets dozens of times farther out than Neptune, and even worlds circling two stars, like Tatooine in *Star Wars*.

Yet perhaps the biggest exoplanetary surprise of all? The super-Earth. This class of planet — loosely defined as any world with up to 10 times Earth's mass — is like nothing in our solar system. Super-Earths fall smack dab into a size and mass gap between Earth and the gassy worlds Uranus and Neptune. Talk about terra incognita.


Nor do super-Earths appear to be outliers. Astonishingly, this species of planet is the most common in the Milky Way, making up some 77 percent of the planetary quarry snagged by our biggest survey to date, with the Kepler space telescope. "We see these planets around every kind of star we look at," says Zachory Berta-Thompson, an observational astronomer at the Massachusetts Institute of Technology. "Clearly nature likes to make them."

In the past few years, a flurry of research has begun shedding light on these unprecedented planets. And the emerging picture is striking. This type of world is the planetary equivalent of Starbucks — everywhere you go, full of near-endless variations. Some, we think, are gaseous orbs, better described as mini-Neptunes. Solid, rocky super-Earths, on the other hand, could be covered completely in oceans of water — or lava. Super-Earths' insides could contain hypercompressed ices that are paradoxically hot or be bejeweled with layers of carbon crushed into diamond. Ice and bling aside, some super-Earths could be just that: supersized Earths, largely indistinguishable from our own Blue Planet, at least from the surface.

This last possibility becomes even more pulse-quickening because super-Earths will be the first worlds we can telescopically probe for alien life. Plain ol' Earth-size worlds, the first of which are now trickling into our exoplanet catalogs, will remain too small for our telescopes to study in any detail for years to come. So ongoing research is delving into super-Earths, from clouds tops to cores, to see if they have the right stuff for life.

"Super-Earths might be just as good as Earth [for life], if not better," says Dimitar Sasselov, director of the Harvard Origins of Life Initiative in Cambridge, Mass. "Super-Earths as a family are the places where we should be looking for living planets."

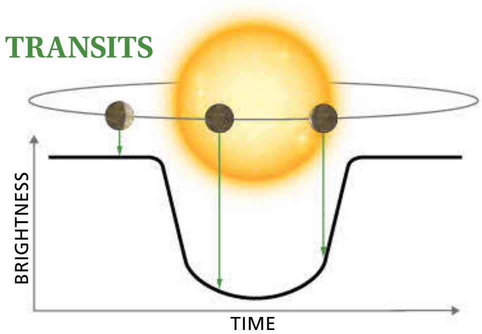
**STRANGE NEW WORLDS**

The newfound significance of super-Earths is ironic, for these worlds have been right under our nose since the beginning. The very first exoplanets, discovered in 1992, are members of this class, although they don't orbit a normal star. Instead, they make laps around a pulsar, the city-size remnant of a colossal star gone supernova, and send out beams of radiation. Discrepancies in these beams from the pulsar PSR B1257+12 suggested the presence of two interfering bodies — *planets?* — each with a mass about three times Earth's.

The finding gobsmacked researchers, including Sasselov, who grew up ogling Jupiter's moons through a backyard telescope in Bulgaria. "We were all wondering, 'What kind of weird things are these?'" he says.

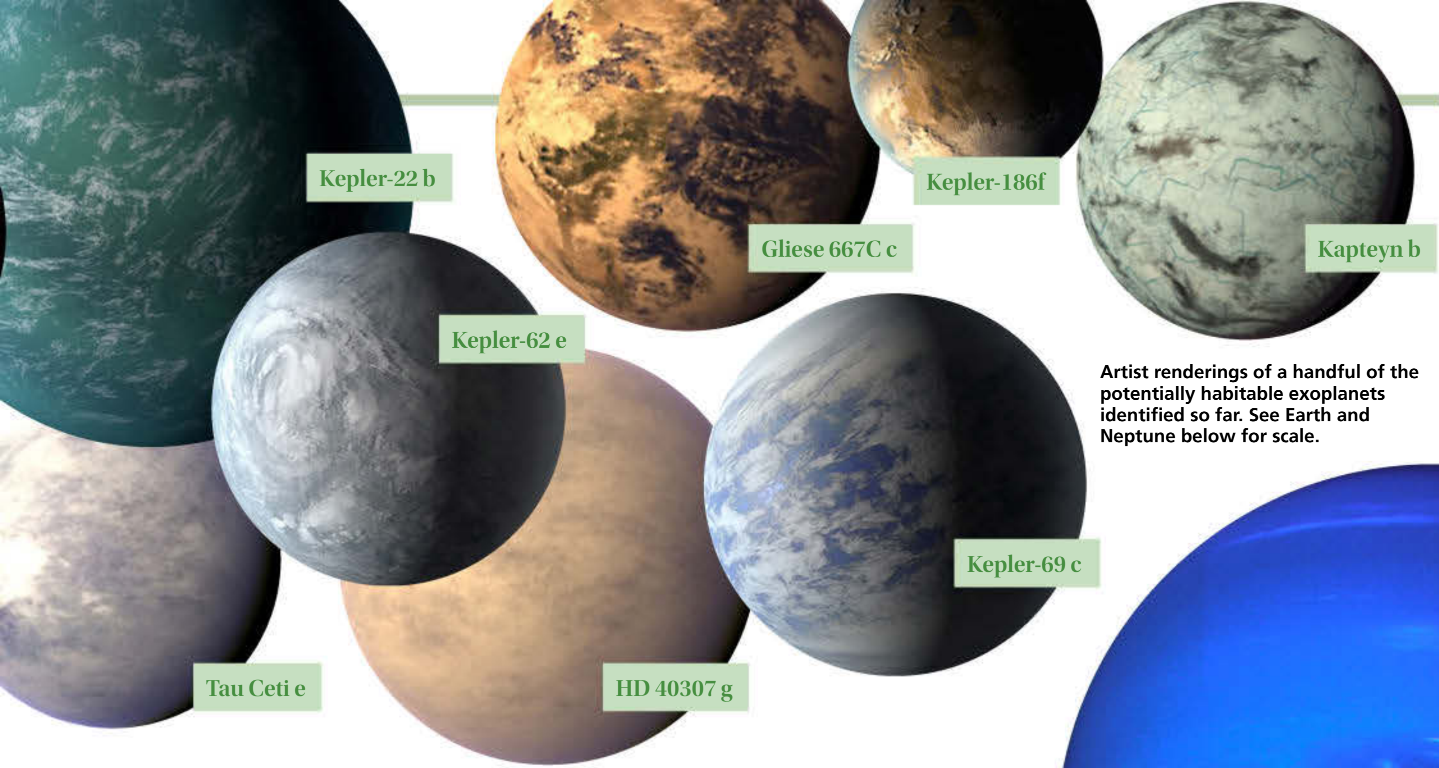
Scientists still debate the pulsar planets' origins, and back then few people took these freakish would-be worlds seriously, anyway. The true exoplanet gold rush didn't kick off until 1995 with the discovery of a so-called hot Jupiter in an infernally close orbit around a typical sunlike star. Finally, a (relatively) normal-looking planet!

## TELLTALE TRANSITS




The shadow of a planet crossing in front of a star creates a measurable dip in brightness. The Kepler space telescope (left) would use that decrease to identify potential exoplanet candidates.

KEPLER PLANETS: NASA AMES/JPL-CALTECH. ALL OTHER PLANETS: PHL@UPR ARECIBO. TRANSIT DIAGRAM: ROEN KELLY/DISCOVER. KEPLER SPACECRAFT: NASA AMES/JPL-CALTECH




**Artist renderings of a handful of the potentially habitable exoplanets identified so far. See Earth and Neptune below for scale.**

Buoyed, astronomers began planning for the planet-harvesting mission that would launch 14 years later as Kepler. Over the space telescope's first run, cut short due to a component failure in spring 2013, Kepler patiently stared at 150,000 stars, looking for the tiniest of flickers as planets crossed their faces — so-called "transits." These crossings not only betray an exoplanet's presence but also reveal its size, based on how much starlight the world blocks.

In 1999, while writing up the Kepler proposal, Sasselov wondered if we might find bigger versions of Earth. For lack of a better term, he blurted out "super-Earth." "I said at the time, 'I don't necessarily want to use that word, so if you have a better option. . . .'" Sasselov recalls. "But people started using it, and now it's become so entrenched."

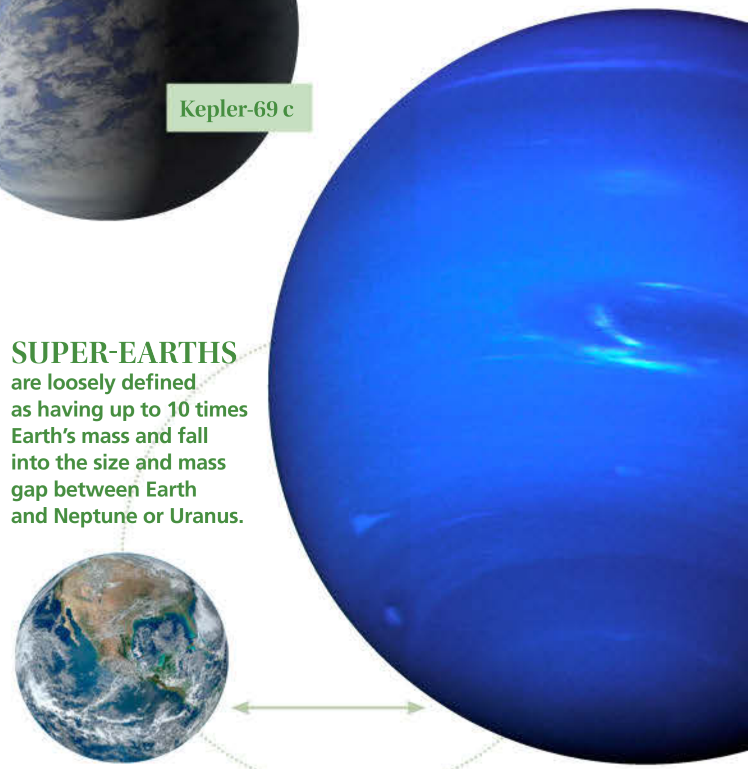
For years afterward, though, even as scores of hot Jupiters piled up, super-Earths remained elusive. Nevertheless, Sasselov, his student Diana Valencia and their colleague Richard O'Connell went out on a limb. In 2004 they submitted a paper speculating on theoretical super-Earths' interior structures. The concepts were so unheard of that the journal editor struggled to drum up peer reviewers with relevant expertise.

A year later, these stabs in the dark paid off when researchers proved super-Earths are not just a funky phenomenon around pulsars. Prior scrutiny of the typical star Gliese 876 had rustled up two Jupiter-size companions, and further research revealed a third body, dubbed Gliese 876 d, pegged at 7.5 Earth-masses — the smallest-mass exoplanet then known.

"Gliese 876 d was really an important threshold event," says Sasselov. The long-in-limbo interior structure paper he co-authored with O'Connell and Valencia was finally published in the journal *Icarus* in 2006, and super-Earth science was born.

For Valencia, this finding came in the nick of time. A

**SUPER-EARTHS are loosely defined as having up to 10 times Earth's mass and fall into the size and mass gap between Earth and Neptune or Uranus.**




EARTH: NASA/JPL-CALTECH. NEPTUNE: NASA

physicist from Colombia, she was captivated by the idea of super-Earths, but "there was no data," says Valencia, now an assistant professor of physics at the University of Toronto Scarborough. A colleague "teased me that I was studying imaginary planets." Seeking a potential backup plan, Valencia took a summer seismology internship at Shell Oil. She was planning to return to Harvard, but the Gliese 876 d discovery sealed the deal. She left the oil industry and returned to her passion, never looking back. "I was lucky," Valencia says. "The stars aligned."

## WHAT ARE YE?

Valencia's excitement proved justified, as ecstatic planet hunters added more super-Earths to the rolls. Yet for several years, scientists knew nothing else about these worlds except their masses. Without a direct analog in the solar system, no one could guess if these newfangled planets were predominantly rocky (Earth-like), gassy (Neptune-like), something in between (water worlds?) or all of the above.



CoRoT-7b (foreground above) is about the size of Saturn and 60 times closer to its sun than Earth is. GJ 1214 b (right) has a cloudy atmosphere of potassium chloride or zinc sulfide.

"That's our first big question about super-Earths," says MIT's Berta-Thompson. "What the heck are they made of?"

For any real insight into these worlds' essences, astronomers needed to find a transiting super-Earth, which would yield a size estimate. Once they knew a planet's size and mass, high school physics would provide its density. (From your old notes: Density equals volume divided by mass.) Knowing an object's density is akin to holding it in your hand as you gauge its weight in relation to its size, explains Berta-Thompson.

"At a very gut level here on Earth, if I want to figure out what something is, I pick it up," he says. "I can say, 'This is made of water, of wood, this is a balloon.'" With densities, scientists could judge super-Earths as fluffballs or medicine balls, as dead or possibly as living worlds. "Bulk density goes a long way to telling you the character of a planet," says University of Hawaii's Howard.

The wait ended in 2009, when astronomers divined the densities of two super-Earths. The first, named CoRoT-7b after the spacecraft that witnessed the transits, weighs about five Earth-masses, measuring about one-and-a-half times Earth's width. The derived density figure confirmed CoRoT-7b as the first truly rocky exoplanet, heralded then as the most Earth-like known, though given the infernal proximity to its star, its surface must be molten.

**With densities, scientists could judge super-Earths as fluffballs or medicine balls, as dead or possibly as living worlds.**

The pendulum swung the other way for the second, to a lightweight called GJ 1214 b, still the most studied super-Earth. "We found it in my first year of grad school," recalls Berta-Thompson, who, daunted by undergrad physics courses at Princeton, nearly became an art history major. "We'd just started this project, and I thought, 'Wow, we're finding planets!'" GJ 1214 b's tale of the tape: about five Earths wide, with six-and-a-half times the mass, and a density several times lower than CoRoT-7b's. The puffy world likely has a huge, gassy atmosphere, perhaps full of scalding water vapor.

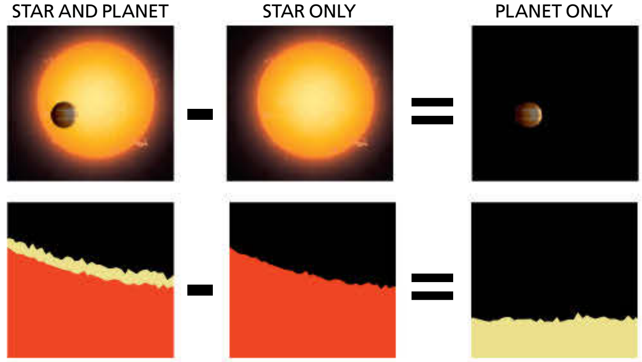
Kepler's recent haul of super-Earths has built on these findings and offered clarity on where super-Earths enter into lifeless mini-Neptunehood. A study last year co-authored by Howard brought the number of super-Earths with known densities to around four dozen. A study later in 2014 by California Institute of Technology's Leslie Rogers concluded that a good rocky cutoff point is a width 3.2 times that of Earth. Below that girth, the planet is dense for its size, and likely rocky. At or above that figure, densities start to drop, despite bigger planetary sizes. Lighter wares — such as water, ice and gases rather than rock — must take up a swelling share of the volume of these larger, less-dense super-Earths.

## THE AIR UP THERE

Pegging a world as rocky or gassy is, of course, only a first step toward assessing if life could call it home. Astronomers are now taking the next step of studying super-Earths' atmospheres directly. During a transit, light from a host star filters through the atmosphere of an exoplanet before being eclipsed by the planet's opaque bulk. Based on the colors of light that reach us, scientists can detect the "fingerprints" of specific molecules. With enough data, they can theoretically reconstruct an atmosphere's overall makeup. The amounts and kinds of gases they observe offer clues not only to whether super-Earths can support life, but if in fact life is already there.

So far, exciting finds such as water vapor, carbon dioxide and methane have been spotted mostly in the mammoth atmospheres of super-Jupiters, which, like super-Earths, are gargantuan versions of worlds familiar to us. Rockier super-Earths have considerably smaller atmospheres, translating to less light reaching our telescopes. The results to date from the Hubble and Spitzer space telescopes have admittedly been underwhelming. Light collected sporadically from nearby GJ 1214 b and from another super-Earth, HD 97658b, are devoid of specific molecules' fingerprints.

But the interpretation of these seemingly boring readings is stirring: These worlds are likely cloud-swathed, like Venus. High cloud decks apparently block light from individual



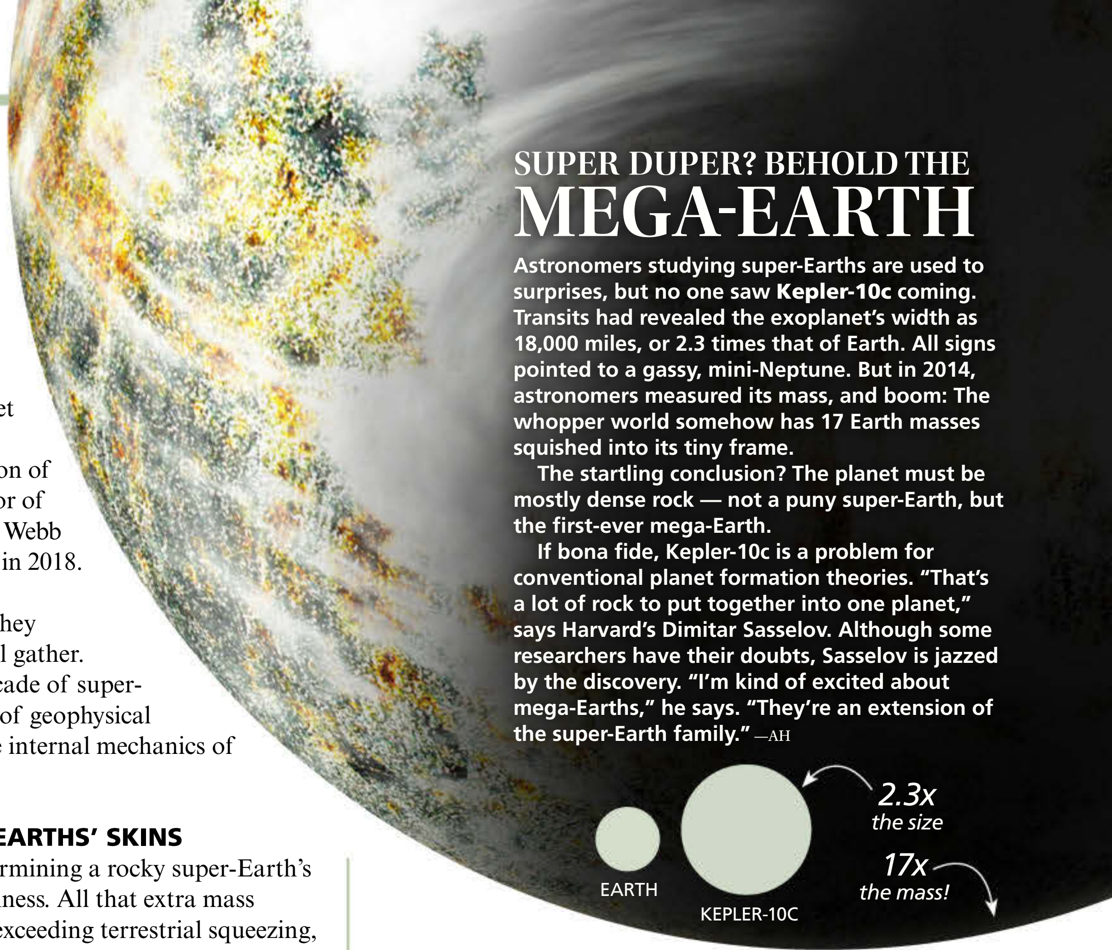

### DECIPHERING DISTANT ATMOSPHERES

**To find an exoplanet's atmosphere, a telescope would record the spectral signature when the planet transits in front of its host star and again when it's behind. The difference shows what molecules exist in the planet's atmosphere alone.**

THIS PAGE FROM TOP: ESO/L. CALÇADA; NASA, ESA AND A. FEILD AND G. BACON (STSCI); ROEN KELLY/DISCOVER AFTER NASA. OPPOSITE FROM TOP: HARVARD-SMITHSONIAN CENTER FOR ASTROPHYSICS/DAVID AGUILAR; NASA

molecules lower in their atmospheres, making it harder to identify them. Astronomers are still working on untangling the clouds' signatures. Overall, it's been good practice for what's to come: Picking apart the molecular makeup of exoplanet atmospheres will actually be a chief goal of the next generation of telescopes, such as the successor of Hubble and Spitzer, the James Webb Space Telescope, set to launch in 2018.

Before JWST goes to work, astronomers want to be sure they can understand the data it will gather. Fortunately, the inaugural decade of super-Earth science has seen plenty of geophysical model-making, simulating the internal mechanics of an Earth on steroids.




## SUPER DUPER? BEHOLD THE MEGA-EARTH

**Astronomers studying super-Earths are used to surprises, but no one saw Kepler-10c coming. Transits had revealed the exoplanet's width as 18,000 miles, or 2.3 times that of Earth. All signs pointed to a gassy, mini-Neptune. But in 2014, astronomers measured its mass, and boom: The whopper world somehow has 17 Earth masses squished into its tiny frame.**

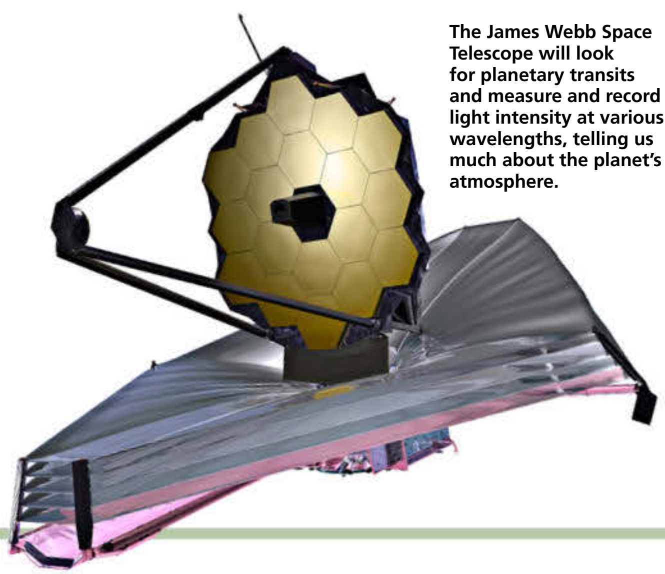
**The startling conclusion? The planet must be mostly dense rock — not a puny super-Earth, but the first-ever mega-Earth.**

**If bona fide, Kepler-10c is a problem for conventional planet formation theories. "That's a lot of rock to put together into one planet," says Harvard's Dimitar Sasselov. Although some researchers have their doubts, Sasselov is jazzed by the discovery. "I'm kind of excited about mega-Earths," he says. "They're an extension of the super-Earth family."** —AH

### GETTING UNDER SUPER-EARTHS' SKINS

The most critical issue in determining a rocky super-Earth's geophysics is its inherent beefiness. All that extra mass creates internal pressures far exceeding terrestrial squeezing, with implications for three life-critical planetary properties: the maintenance of oceans, climatic "thermostats" and magnetic fields.

These three phenomena all relate to what's happening inside a planet. Take Earth, for instance. As the fledging world cooled from its initial molten state over hundreds of millions of years, its outermost layer solidified into a crust. This then cracked apart into plates, which bump and grind atop a warm, denser mantle region, surrounding a still-denser, molten metal layer. Beneath everything hides a solid iron core. Heat spewing from this region roils the mantle, like a burbling fondue pot. The crust's plates dive underneath each other, plunging back into the mantle (triggering earthquakes) and melting down. Likewise, ocean water recycles through Earth's mantle at a sufficient rate to maintain our world-spanning seas for eons. Both rock and water return to Earth's surface through the volcanic cracks between the plates, perpetuating the cycle.



**The James Webb Space Telescope will look for planetary transits and measure and record light intensity at various wavelengths, telling us much about the planet's atmosphere.**

So far, so Earth-centric. What of super-Earths? Taking the matter of oceans first, models of super-Earth geology in a study co-authored by Sasselov earlier this year found that, yes, super-Earths could be hulking Blue Planets. They should preserve their oceans for billions of years, as well as or better than Earth, owing to adequate mantle recycling of water.

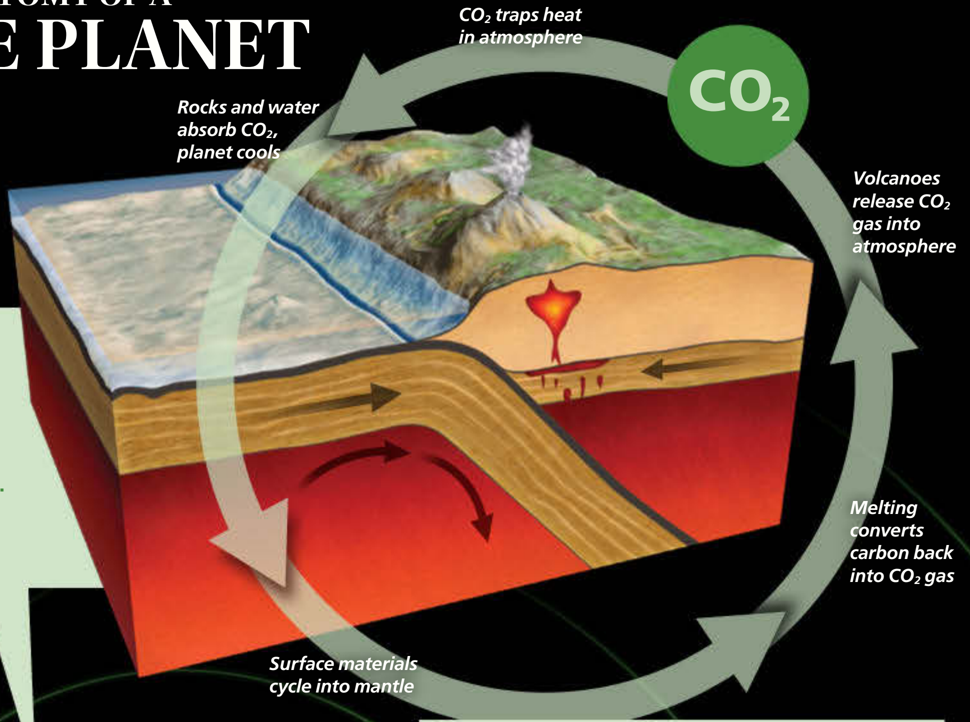
This cycling, enabled by plate tectonics, also influences whether super-Earths can have livable climates over long epochs. The key here is carbon dioxide, a greenhouse gas that traps heat from efficiently escaping into space. Rocks and seawater both absorb carbon dioxide from the atmosphere, sequestering away the heat-trapping carbon and cooling the planet. As these surface materials cycle into the mantle, the carbon is converted back into carbon dioxide gas and is returned to the atmosphere via volcanoes in a self-regulating process: When carbon dioxide levels in the atmosphere climb, more gas gets soaked up by rocks and water, curbing the literal degrees of planetary warming. This carbon sequestration diminishes, however, when lower carbon dioxide levels prevail, preventing a planetary chill from getting too deep. The upshot: Earth self-regulates its global temperature.

Do super-Earths also possess this thermostat? In October 2007, Valencia and her Harvard colleagues published a paper theorizing super-Earths have more active plate tectonics. Higher internal heat should overall create faster convection —

## INSIDE & OUT: THE ANATOMY OF A

# HABITABLE PLANET

**Having an atmosphere isn't the only key to a planet's habitability. Whether it can support a livable climate depends on three life-critical planetary properties.**

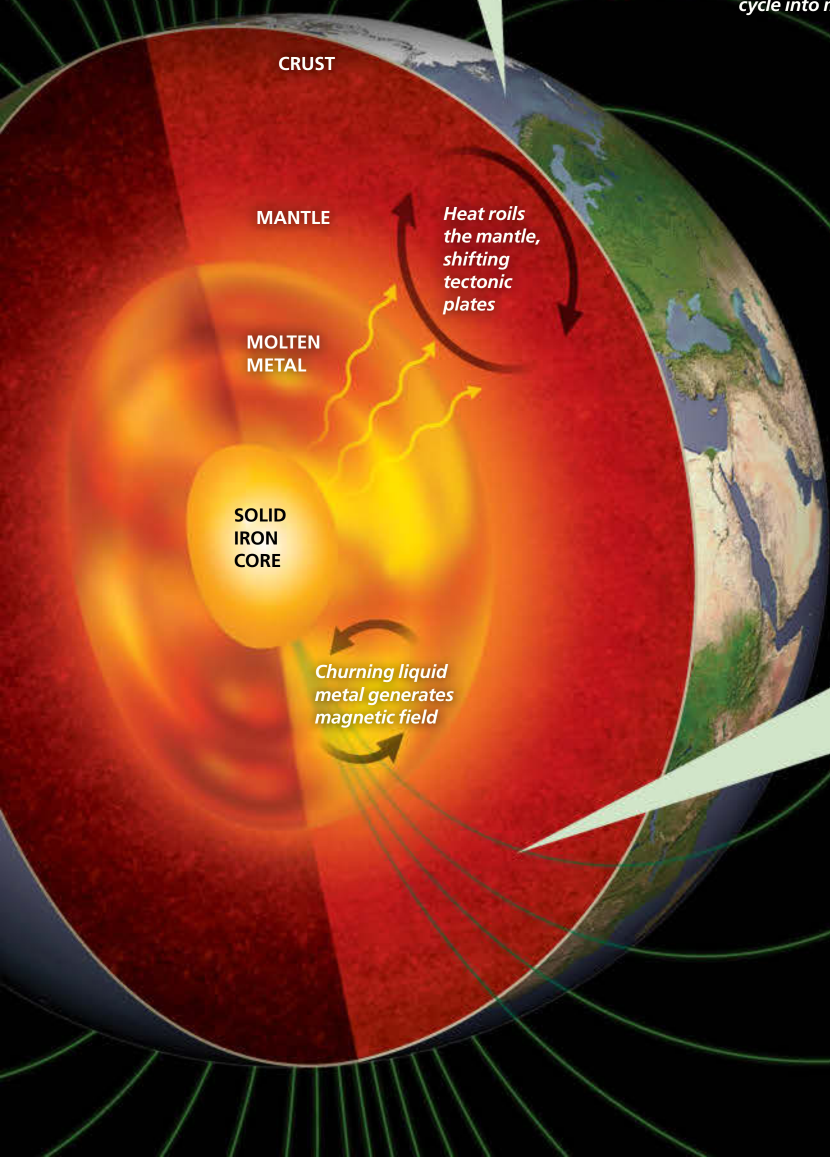



### 1. Maintenance of Oceans

Earth's oceans — a thin film of surface water, really — formed and persist in part thanks to water moving at a sufficient rate through the mantle and back above ground. Models suggest super-Earths could establish and preserve oceans even more successfully than Earth.

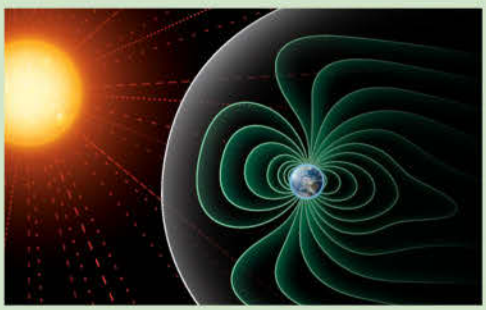
### 2. Carbon Cycling

Heat-trapping carbon dioxide in the atmosphere is thermostatically regulated owing to absorption by rocks and ocean water cycling down into the mantle, followed by relinquishing of carbon back into the air through volcanoes.




### 3. Magnetic Field

A magnetic field deflects harmful space radiation from our planet's surface. Super-Earths might not possess Earth's field-generating outer core of liquid iron and nickel, but other metals could do the job.



that fonduelike mantle circulation. “The convection is more vigorous and the forces are larger, so it seems like it’s easier to have plate tectonics compared to Earth,” says Valencia. Such “super” tectonics would keep atmospheric carbon levels in check, meaning these worlds have more even-keeled climates than Earth. That same month, however, another paper suggested the opposite: Super-Earths’ stronger gravity dominates and keeps the crust from cracking into separate plates in the first place. Ergo, no tectonics, and quite possibly, no life. Eight years later, the matter remains unsettled, with subsequent research supporting both conclusions, though Valencia notes that more researchers suggest plate tectonics are possible.

Yet another big question mark on super-Earth habitability, stemming from planetary interiors, is the presence of a magnetic field. Earth’s field deflects much of the sun’s radiation that likely would have ended any upstart life. The sloshing of our world’s interior liquid-iron layer generates this shield. Higher pressures in super-Earths, however, would lead to higher melting temperatures. The planets’ interiors might stay solid and not separate out into Earth-style layers, according to a 2011 study. No liquid metal layer equates to no magnetic field, and no life.

But a separate study that year pointed to another possibility: The higher heat might melt magnesium oxide, a common mineral used in ceramics, and one that would be expected in ample quantity within super-Earths, too. This mineral, when liquefied and churning, could crank out a magnetic field.

**By knowing which super-Earths are rocky and have geophysics conducive to life, astronomers can choose ideal targets for biosignature studies with next-generation instruments.**

Clearly, we need a better grasp of super-Earths’ inner workings to size up their habitability, and Sasselov’s research group continues to explore the possibilities through computer simulations. “We’re not simply running Earth-like interiors for bigger planets,” he says. “It involves some very interesting new physics.” New papers in the works will also sketch out how super-Earths’ insides influence the release of detectable gases into the atmosphere. As one example, learning the carbon dioxide abundance in a super-Earth’s atmosphere would help astronomers gauge whether it’s a temperate place or more like Venus, whose thick carbon dioxide atmosphere conspires with its solar proximity in raising its surface temperature to 900 degrees Fahrenheit.

## LIFE’S SIGNS

Theories and models of livable climates are one thing, but Sasselov and his colleagues ultimately seek far bigger quarry: actual evidence of alien life. To find that, they need to figure out the combinations of gases, known as biosignatures, that could plausibly be produced only by life. A common example is methane in the presence of ample oxygen, as in Earth’s atmosphere. Typically, oxygen breaks down methane rapidly, and it also seeps into rocks (like carbon dioxide), so for both gases to endure in an atmosphere, something —

During its two-year mission, the Transiting Exoplanet Survey Satellite (TESS) is expected to monitor the brightness of more than 500,000 stars and catalog more than 3,000 possible transiting exoplanets, according to NASA.

likely biological — must keep putting them there.

“It’s this jewel of an idea, that life can really profoundly influence an exoplanet’s atmosphere,” says Berta-Thompson. “That’s so compelling when linked with the fact that we know how to study the atmosphere of a planet many tens of light-years away.”

By knowing which super-Earths are rocky and have geophysics conducive to life, astronomers can choose ideal targets for biosignature studies with next-generation instruments. And “targets” is the name of the game with the Transiting Exoplanet Survey Satellite (TESS), launching in 2017 and spearheaded by MIT. TESS will zero in on exoplanets transiting nearby bright stars — the easiest to study. Perhaps 20 objects in TESS’ anticipated planetary windfall should be super-Earth-caliber planets in the “habitable zone.” This is the not-too-hot, not-too-cold orbital distance from a star where life has a chance. “TESS is going to be a fire hose of incredible new planets,” says Howard. “It’s going to be a great machine.” JWST, meanwhile, will focus on the best candidates pinpointed by TESS and other surveys. New, huge ground observatories with mirrors a hundred feet across (nearly four times the size of today’s largest) will also join the party when they see first light in the 2020s.

Berta-Thompson can’t wait. “Even if these telescopes don’t tell us, ‘This is a planet covered in green slime,’ they will push us much farther down the road to that ultimate goal of finding life around other planets,” he says. “My wife is a microbiologist. She studies photosynthetic microbes in the ocean. My hope is that by the time we finish our careers, we’re working in the same field.”

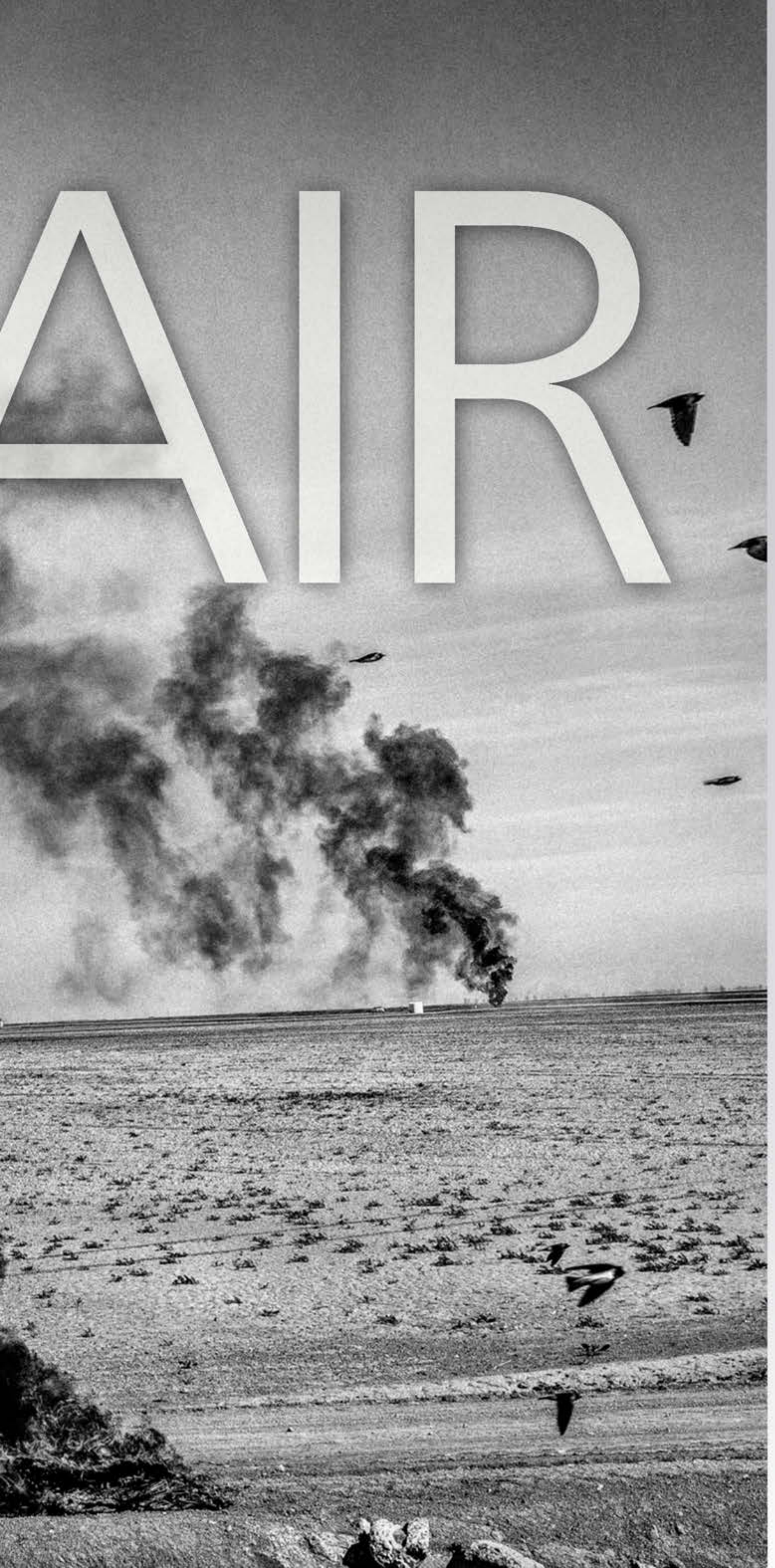
If the history of exoplanet investigation is any guide, we should also expect surprises aplenty as we sink our teeth into super-Earths. “Nature is much more imaginative than we are,” says Valencia. “These planets really are a testament to that.” D

***Adam Hadhazy** is a freelance science writer based in New Jersey. He also frequently contributes to* BBC Future *and* Astrobiology Magazine.

OPPOSITE: EARTH CUTAWAY AND MAGNETIC FIELD INSET, ROEN KELLY/DISCOVER; TECTONIC PLATES DIAGRAM, ANDREA DANTI/SHUTTERSTOCK. THIS PAGE: NASA/GSFC

# SOMETHING IN THE A

Smoke from burning tires, used to help guide crop dusters, wafts through California's Central Valley. Its air is among the most polluted in the state.



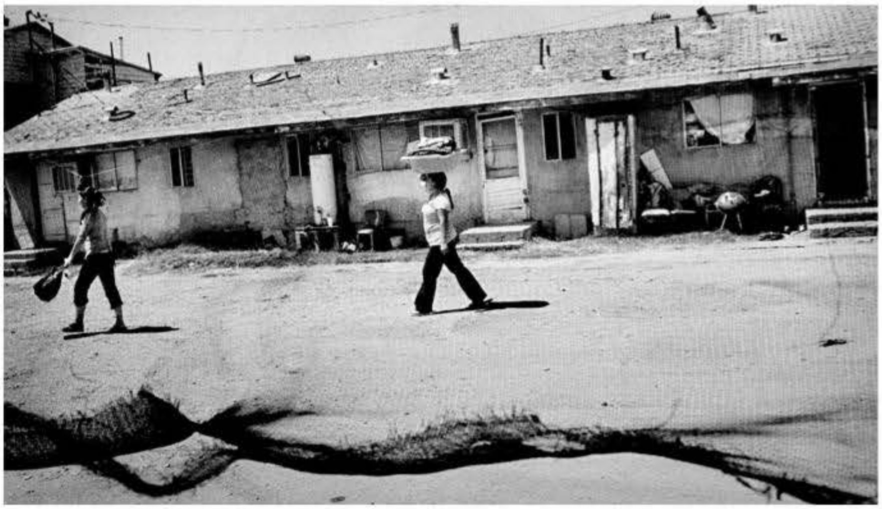

## Can one California community's pollution spur genetic changes that lead to generations of asthma?

BY **MELISSA PANDIKA**
PHOTO BY **MATT BLACK**

As pediatrician Kari Nadeau and I leave California's Pacheco Pass and head east, the Bay Area foothills give way to acres of orchards and level farmland. After three hours in the car, the jagged contours of the Fresno metropolis appear stark against a clear sky — but only because the cold air had pushed the hazy, gray smog below the horizon, Nadeau explains. She stops midsentence as the truck ahead of us coughs a cloud of black smoke. "Did you see that?" she says, eyes widening, her voice rising with a blend of awe and disgust.

Nadeau, who specializes in asthma, is heading to Fresno to meet with other researchers working on the San Joaquin Children's Health and Air Pollution Study. It's a trip she makes about every three months. In Palo Alto, where she lives in an airy, two-story home with her husband and five kids, she sees asthma patients a few times a week at Stanford's Lucile Packard Children's Hospital. Most of the children live in Palo Alto, but a few journey from Fresno for care they can't get back home.

As we near the outskirts of the city early that afternoon, caravans of big rigs with soot-streaked trailers groan past. Not far away, dusty-faced migrant workers and their families, as well as homeless people, live in vast shantytowns — rows of tents, and shopping carts, sofas and bicycles



Residents return home from a laundromat in Mendota, Calif., about 40 miles west of Fresno. More than 26 percent of Fresno County's 1 million people live in poverty, the state's highest rate in 2010.

strewn about. Although it is the most profitable agricultural area in the nation, Fresno County had the highest poverty rate in California in 2010, with 26.8 percent of its nearly 1 million residents living in poverty. Fresno-Madera ranks as the metropolitan area with the highest exposure levels to particle pollution, or soot, in the country.

Palo Alto and Fresno might as well be different worlds. And Nadeau has discovered a difference of extremes in the lungs and genes of her patients as well. She found that kids in Fresno were more likely to develop asthma not due to lung damage, but because changes on the surfaces of just two genes — and likely more — altered the way their lungs worked.

These two genes are crucial for tightening the reins on the immune system to prevent it from reacting to benign agents and triggering asthma symptoms. Unlike mutations, these changes to the surfaces of genes — part of what's called epigenetics — alter how those genes behave without rewriting the information they encode. It's like tagging them with Post-It notes that tell a cell to switch a gene on or off. Nadeau has discovered that in the Fresno children, long-term exposure to air pollution and secondhand smoke switched off two specific genes. Similar changes happened in the Palo Alto children, but at significantly lower rates.

Nadeau believes heavy pollution causes asthma-inducing epigenetic changes that can last a lifetime — and even transcend generations. That connection took years for Nadeau to make. The question now is whether this insight might someday lead to treatment of the disease.

## A RIGHT TO BREATHE

Nadeau, 49, knows asthma especially well — she's been living with it since about age 3. Back then, she dreaded bedtime. Each night, she'd sit upright for as long as possible, a nebulizer with asthma medication strapped to her face, on guard for an asthma attack: the heavy, searing pain; the panic of gasping for air. Living for a couple of years on a houseboat off the smog-laden Newark, N.J., shore didn't help. By elementary school, Nadeau had accepted breathing problems as a reality — one that persists to this day. She knew asthma attacks could kill her.

Nadeau's asthma inspired her to become a doctor. As an undergraduate, she helped build a medical clinic and sewage system in Nicaragua. The impact stuck with her. At Harvard Medical School, she wanted to give fellow students the same opportunity to protect people's right to health care on a global level, launching a partnership between the university and Physicians for Human Rights.

**"It really hit me. The kids were placed in this situation. They had no control whatsoever."**

Nadeau had gotten reports of a tuberculosis outbreak among children at a federal immigration detention center in Harlingen, Texas. It didn't make sense that kids' infections would spur an outbreak; they typically didn't have the strength to cough up the contagious mucus from deep in the lungs. So in the fall of 1994, she flew to Harlingen.

A 14-year-old patient of Kari Nadeau takes a spirometry test, which assesses lung function, at a clinic in Mountain View, Calif.

When Nadeau entered the looming white building and peered into the barracks, she saw children piled onto rows of Army-style bunk beds — and among them, adults who had seeded the outbreak and were crowded out of their own quarters. The cramped conditions created the perfect breeding ground for TB-causing bacteria.

"It really hit me," says Nadeau. "The kids were placed in this situation. They had no control whatsoever." After she detailed her findings in the *Western Journal of Medicine*, the center moved the adults back to their facility. She realized then her power as a doctor to advocate for children who have no say in their environment.

After Harvard, Nadeau worked as a resident specializing in pediatric blood diseases and cancer at Children's Hospital of Boston. Emotionally spent, she worked for a biotech company for a few years. She left the corporate world and landed a fellowship in 2008 in allergy, asthma and immunology at Packard Children's Hospital.

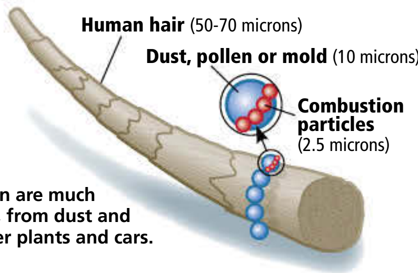
Nadeau studied immune cells called regulatory T cells, or T-regs. They are what they sound like: regulators that

TOP: MATT BLACK. BOTTOM: PETER DASILVA

Soot hangs in the air in Fresno. Air pollution appears to worsen how two genes function, which can lead to asthma symptoms.

## Breathing in Bad Air


Four out of five of the metropolitan areas with the highest levels of both short-term and year-round particle pollution are in California's Central Valley area, according to the American Lung Association's 2015 State of the Air report.




Particles that make up air pollution are much smaller than a human hair (right), from dust and mold to those emitted from power plants and cars.

keep another group of cells, T helper cells, from proliferating out of control. Think of T-regs as police officers, keeping a tight leash on T helper cell attack dogs. We need T helper cells; they kick-start the immune system to respond to potential invaders. But too many can move the immune system into overdrive, evoking coughing, airway constriction, mucus production and other asthma symptoms.

Suspecting that the T-regs in asthma patients didn't function as well as they did in healthy people, Nadeau isolated T-regs from adult and pediatric patients' blood samples and tested their ability to suppress T helper cells. The policing T-regs from most of her 200 patients kept T helper cells at bay. But 30 had poorly functioning T-regs that let T helper cells proliferate unchecked. They also had worse asthma symptoms. One girl couldn't leave her house without triggering an attack, while a boy had allergies so severe that he had to seek disability status.

Skeptical, Nadeau repeated the experiments, yet the same 30 patients surfaced. Did they have the same ethnicity or socioeconomic status? No and no. It's got to be some environmental exposure, she thought, perhaps something to do with where they lived in Palo Alto.

Nadeau looked up her pediatric patients' ZIP codes. Those 15 children weren't from Palo Alto. They lived in Fresno, a city she soon learned had high levels of air pollution — mostly diesel exhaust from trucks, cars and tractors — in contrast to Palo Alto's clear skies. She had a strong hunch that this pollution had disabled T-reg function in her Fresno patients.

But her sample size was still small enough that she couldn't rule out a statistical fluke. So she cold-called Ira Tager, a now-retired environmental epidemiologist at the University of California, Berkeley, with her findings in 2008. For the past decade, Tager had been running a large-scale study in Fresno looking at how pollution affects the lungs.

He found Nadeau's results fascinating and invited her to visit him in Berkeley. The two hit it off, and he agreed to let Nadeau collect blood from his Fresno subjects to check whether pollution had worsened their T-reg function, too.

As part of Nadeau and Tager's study, participants completed questionnaires about their exposure to pollution and secondhand smoke. Air quality monitoring and statistical modeling measured each person's pollution exposure.

Now Nadeau had a larger patient pool that included children with and without asthma in Fresno and Palo Alto. She saw the best T-reg function in Palo Alto kids without asthma. Even Palo Alto children with asthma had better T-reg function than Fresno children without the disease. And, sure enough, Fresno children with asthma had the worst T-reg function.

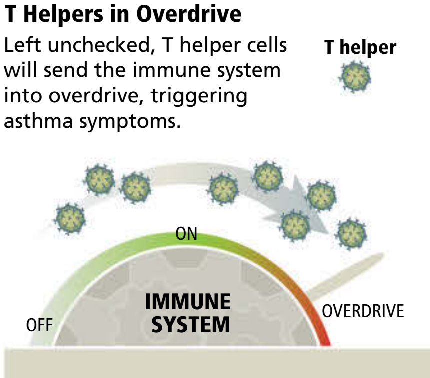
To figure out the mechanism, Nadeau focused on the gene *Foxp3*, which spurs immature T cells to develop into those police officer cells, T-regs. Research had shown that children born without *Foxp3* suffered from asthma, allergies and autoimmune diseases. Nadeau stumbled upon one study, in mice, describing how environmental factors can tag *Foxp3* with chemical markers that tell T-cell precursors to switch the gene on or off. Tagging *Foxp3* with a methyl group is like sticking a Post-It note on it that says "off." An acetyl group's Post-It note says "on."

"That paper changed my life," Nadeau says. "If this is happening in mice, it's probably happening in humans." Some studies also suggest that these epigenetic changes are heritable.

Once Nadeau understood the role of the methyl groups in gene expression, all the dots began to connect. She believed that air pollution triggered asthma in her Fresno patients by tagging *Foxp3* in

### T Helpers in Overdrive

Left unchecked, T helper cells will send the immune system into overdrive, triggering asthma symptoms.




CLOCKWISE FROM TOP LEFT: ZUMA PRESS INC./ALAMY; ALISON MACKEY/DISCOVER; JAY SMITH

immature T cells with methyl groups, switching off its expression. This prevents the cells from maturing into those police officer T-regs that hold T helper cells in check. More exposure to pollution, then, would mean more methyl groups.

As it turned out, *Foxp3* bore the fewest methyl groups in Palo Alto children without asthma, and more in Palo Alto children with the disease. In Fresno children without asthma — who had grown up with more pollution — the gene had still more methyl groups. *Foxp3* bore the most methyl groups in Fresno kids with asthma. "It seemed amazing for just one molecule to be standing out," Nadeau says.

Nadeau and Tager published their results in the *Journal of Allergy and Clinical Immunology* in 2010. Meanwhile, researchers at Columbia University, the University of Cincinnati and other institutions began publishing similar findings. But the trend was troubling: Pollution's imprint wasn't unique to Fresno. Scientists were seeing the same effects in polluted cities across the country.

**Pollution's imprint wasn't unique to Fresno. Scientists were seeing the same effects in polluted cities across the country.**

## SMOKE SCREEN

Nadeau's findings revealed that pollution could cause asthma by altering our biology at a fundamental level, changing how our very genes behave. After the 2010 paper was published, she wondered, could secondhand smoke have a similar effect? It also can lead to asthma, and research had shown that children, especially those living in poor communities like Fresno, are especially vulnerable to secondhand smoke. Nadeau wanted to unravel how exposure to it affected methylation and gene expression. Scientists had already found that smoking could cause epigenetic changes. But what were those changes? And how might they trigger asthma?

In a small office in Nadeau's clinic, Arunima Kohli, an undergraduate in her lab, was sifting through the questionnaire and pollution data that Nadeau and Tager collected. Since the questionnaires asked about participants' secondhand smoke exposure, Nadeau asked Kohli to include the responses in the analysis of their immune cells. *It's right at our fingertips*, Nadeau thought.

Nadeau wanted to examine how air pollution and secondhand smoke — both linked to asthma — spurred epigenetic changes to *Foxp3*. And if these stressors epigenetically altered *Foxp3*, they probably affected other genes regulating the allergic pathway, too. Since studies had shown that children in heavily polluted areas of the Central Valley had more infections, and pollution and secondhand smoke contain similar toxic compounds, Nadeau searched for genes that played a major role in fighting infection. Understanding how they worked might help point the way to therapies that treat them. She also sought out genes that controlled the switch for maturation of T helper cells, maintaining just the right balance of T helpers — between Th1 cells that suppress allergic responses and Th2 cells that trigger them.

Nadeau finally landed on the protein-coding gene interferon gamma, important in not only fighting infection, but also maintaining the delicate balance of T helpers. When interferon gamma is covered in methyl groups — or switched off — it tips the balance, spurring the development of Th2 cells and sending the immune system into overdrive.

Nadeau suspected that Fresno kids were getting a double whammy of Th2 cells. Not only did they have low interferon gamma expression, they also had low *Foxp3* expression, meaning they had fewer T-regs to police the T helpers. Nadeau suspected the bodies of Fresno children teemed with Th2 cells that triggered asthma.

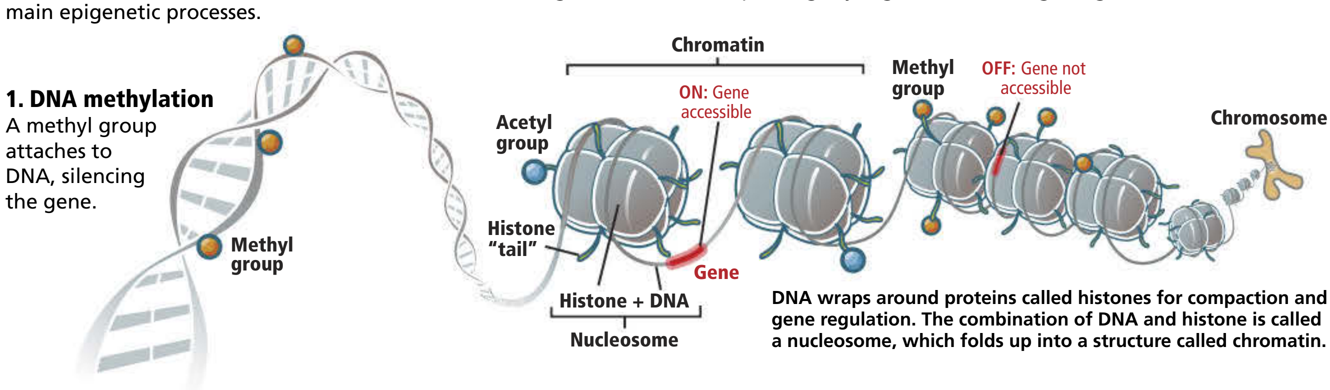
It meant pollution and secondhand smoke might have a synergistic effect. To test this, Kohli plotted each child's amount of exposure to pollution and secondhand smoke against the methylation and expression levels of *Foxp3* and interferon gamma.

Gradually, a picture emerged. The highest methylation and lowest expression of these two genes were found in Fresno patients exposed to both secondhand smoke and pollution. But before Nadeau could get excited, she needed to repeat the analysis; she

## Flipping the Switch

The addition of certain chemical markers can turn a gene on or off via one of two main epigenetic processes.

**2. Histone modification**
Epigenetic markers attach to the histone tail. An acetyl group causes the chromatin to unfurl, exposing the gene for transcription. Methyl groups have the opposite effect, causing the chromatin to pack tightly together, rendering the gene inaccessible.




DNA wraps around proteins called histones for compaction and gene regulation. The combination of DNA and histone is called a nucleosome, which folds up into a structure called chromatin.

THIS PAGE: JAY SMITH. OPPOSITE FROM TOP: PETER DASILVA; JAY SMITH

Pediatrician Nadeau talks with a teen patient at a clinic in Mountain View, Calif.

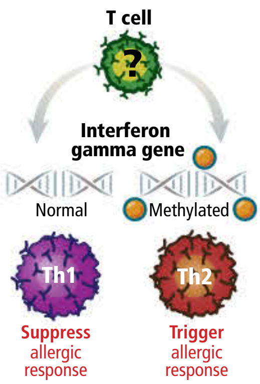
needed to be sure. She handed the data to Tager, a statistician and another lab. Each calculated the same results.

"Then we knew, oh my gosh, this is really real," Nadeau says.

For years, studies had shown evidence that pollution caused asthma and that the disease tends to occur within families. Now, Nadeau and Kohli's results, published in *Clinical Epigenetics* in fall 2012, suggested an underlying mechanism. They also linked two of tobacco smoke's effects — methylation and asthma — suggesting that smoke-induced epigenetic changes could cause asthma as well.

## ALL IN THE FAMILY

But the molecular scars that pollution and secondhand smoke leave behind might not end with the person exposed to them. Research suggests that they can be passed on to children and grandchildren, meaning it may take generations to see their full toll. A 2012 *Biomed Central Medicine* study found that both the offspring and grand-offspring of pregnant rats exposed to nicotine developed asthma even if those descendants had no exposure to the chemical.




Methylation switches off the gene, upsetting the balance of T helper cells.

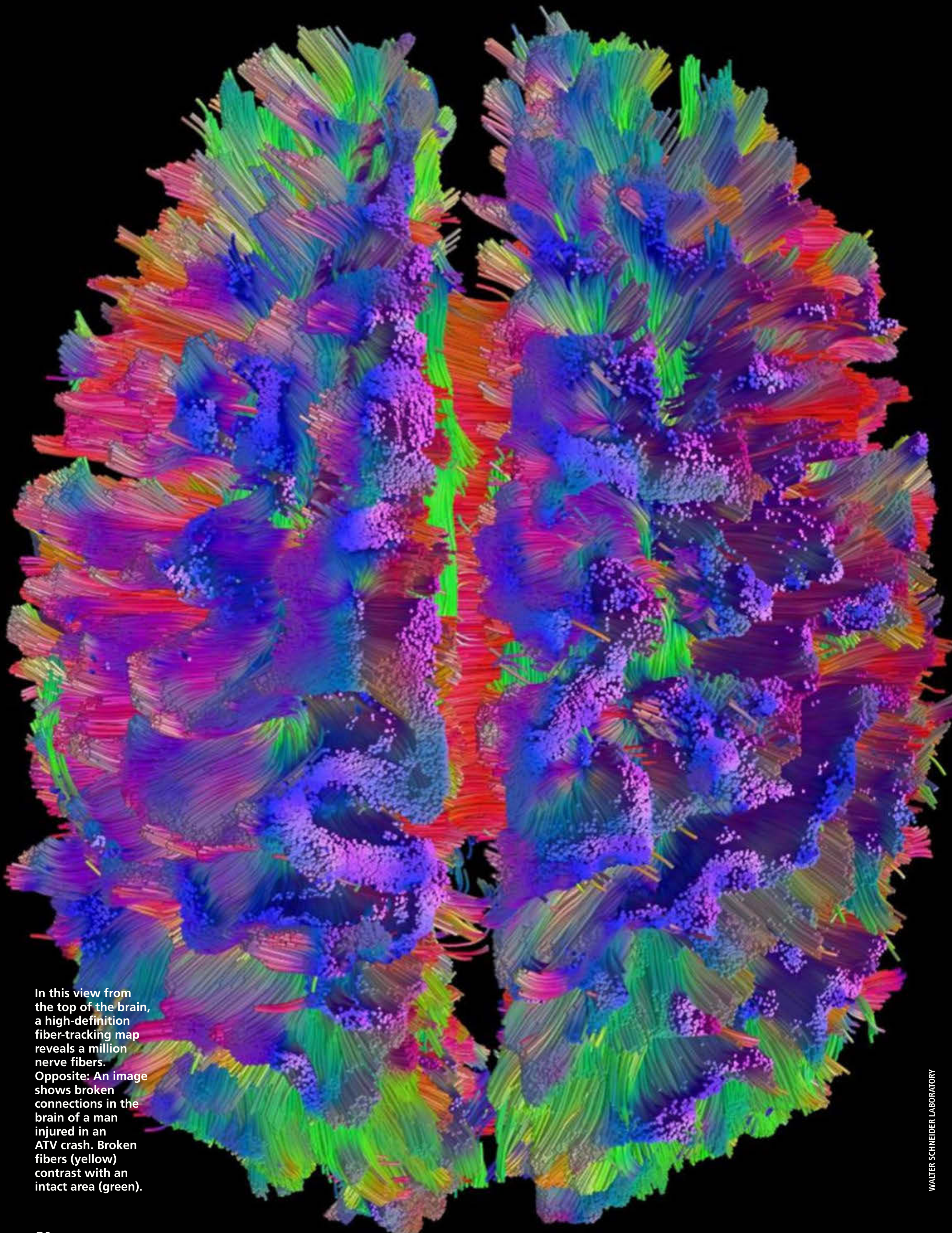
Nadeau gave a human analogy. Imagine a mother who smokes around her infant daughter, causing epigenetic changes in her daughter that persist into adulthood, even if she moves away. When she has her own child, "that grandchild will have the same epigenetic changes the grandma had because of smoking," Nadeau says.

But unlike with genetic mutations, we can "undo" bad epigenetic modifications. The more we understand the mechanisms underlying what makes individuals vulnerable or resilient, the better researchers can design interventions. Nadeau's team is working to identify signaling proteins in the T-reg pathway, as well as develop a screen to predict allergy and asthma prognosis by measuring the ratio of various biomarkers, including *Foxp3* and interferon gamma expression. Preliminary data from another study of theirs suggest that Fresno youth, by moving elsewhere to attend college, might see a reversal of some epigenetic changes to their immune cells. So far, epigenetic changes to these cells have persisted for a year. "But we're still going to test that out long term," Nadeau says.

Some bioethicists doubt that even the most compelling research on the intergenerational impacts of pollution would persuade lawmakers to enact further reforms. "We are not particularly good stewards of the planet or for the people who come after us," says Mark Rothstein, a bioethicist at the University of Louisville School of Medicine.

Even so, like parents who are driven to do something, anything, when their kids are suffering, Nadeau can't sit back and relax, knowing that her work has a chance of helping kids overcome a diagnosis resulting from chance, not choice. "Children don't deserve to suffer," she says. "We need better drugs than when I was a kid, and I'm not going to stop until I get there. No one should watch their kid die." D

*__Melissa Pandika__ is based in the San Francisco Bay Area and frequently writes for OZY, a digital magazine.*



In this view from the top of the brain, a high-definition fiber-tracking map reveals a million nerve fibers. Opposite: An image shows broken connections in the brain of a man injured in an ATV crash. Broken fibers (yellow) contrast with an intact area (green).

WALTER SCHNEIDER LABORATORY

# Broken Cables

**High-definition imaging helps researchers map the damage from traumatic brain injury with unprecedented accuracy.**

**BY BIJAL P. TRIVEDI**

It was a frigid 17 degrees when Louis "Tom" Freund was descending a three-legged communications tower in a hayfield in Ohio. At 40 feet up, he had a splendid view of the frosted brown stalks stretching to the horizon where the cold earth met a cloudless winter sky. Tom was at the top of his game: At 42, he was running a multimillion-dollar company providing broadband Internet access to rural areas. He'd just remarried and was in superb physical shape, capable of clambering up 250-foot-high towers with 40 pounds of tools on his back, leaving colleagues half his age in his wake.

But on this day, Feb. 16, 2009, a weld snapped underfoot — something no amount of experience or physical prowess could have prevented. "I heard a loud ping, and I knew I was coming down," he remembers.

Slicing through the icy air, he watched as the tower toppled away from him. He rode it part of the way down and at the last minute, twisted, catlike, to avoid being crushed. His aerial acrobatics saved his skull from smashing into the steel girders a moment later. The tower hit the ground, then he hit the tower, his chest smashing onto the icy metal frame. His shoulder and the right side of his head slammed into the ground. Even though a bright white haze clouded his vision, he remained conscious. "All I heard," Tom explains slowly, "was a freight train siren going off in my head. It was deafening."

The impact shattered his pelvis and his shoulder, broke the ribs on his right side and damaged his spine and neck. Two lobes of his lungs exploded. As he lay on the frozen ground, which served as a big ice pack, a local medic called to the scene by Tom's assistant gave him oxygen until a helicopter flew him to Allegheny General Hospital in Pittsburgh. He faded in and out of consciousness. The medics forced him to talk to his wife and kids over the radio, convinced he wouldn't survive.

At the hospital, doctors used a CT scan to search for brain bleeds and fractures, which appear white against the fuzzy gray brain structures. Miraculously, the scan was negative. After just four days in the hospital — during which doctors successfully stopped Tom's internal bleeding from punctured lungs and set his broken bones — he was discharged. The rest of his recovery, the doctors told him, was "an orthopedics job." They said his brain was fine.

But Tom didn't feel fine. He was confused, like he was in "the middle of a whirlwind," with thoughts whizzing by that he had to grab before he could verbalize them. His sense of time was distorted. He suffered from raging headaches. His vision blurred as the day wore on, and a siren wailed in his head. He was at a constant loss for words and could not edit his thoughts, often blurting out inappropriate comments. Tom was angry, in pain, and couldn't think clearly.

To this day, he says, his short-term memory is "nil to none," and as we speak, he warns me that he probably won't have any recollection of our conversation. "I don't remember people that I've met a week ago," he says.

For the first three years after the accident, Tom and his wife, Karen, searched for a plausible diagnosis. He visited a series of neurologists, each of them assuring him that he had not sustained brain damage. Next, he sought out psychiatrists and psychologists who told him he had post-traumatic stress disorder (PTSD) — extreme anxiety attacks

**Walt Schneider (above) stands near a high-definition imaging machine used in his work at the University of Pittsburgh Schools of the Health Sciences. He and neurosurgeon David Okonkwo (left) teamed up to develop imaging that creates a wiring diagram of the brain's neurons.**

that recur after a traumatic event. But neither he nor Karen, an emergency room trauma nurse, thought the diagnosis fit.

In the end, it wasn't a doctor who finally identified what was wrong. An attorney who was handling Tom's civil case suggested he had suffered a traumatic brain injury (TBI). He'd seen the same symptoms in football players he'd represented in court. It happens when the head is bumped or struck, like when a football player — or a man plummeting from 40 feet up — hits the ground. Jolts (like in a car crash) or exposure to a blast (which has affected countless soldiers

**Potential injury in a patient's brain isn't visible with a structural MRI (left), but high-definition fiber tracking (right) reveals asymmetry in the corona radiata brain tract. The right (colored red) is smaller, consistent with the loss of motor control on the patient's left side.**

OPPOSITE FROM LEFT: UNIVERSITY OF PITTSBURGH MEDICAL CENTER; SCOTT GOLDSMITH. THIS PAGE: WALTER SCHNEIDER LABORATORY

who served in Iraq and Afghanistan) can also cause TBI.

These kinds of injuries can snap fragile nerves in the brain that carry signals from one part of the body to another. But there is no diagnostic technique that can visualize which nerve fibers, or neurons, are broken. When a nerve snaps, communication between different brain regions is disrupted, just like a damaged circuit in a computer. Not being able to locate the damage is an enormous setback to recovery and rehabilitation for the approximately 1.7 million people who suffer TBI each year in the U.S. That number doesn't include the more than 300,000 soldiers with brain damage inflicted during military combat between 2000 and 2014.

Often such damage is invisible on CT scans, which use X-rays to visualize blockages, bleeds, tumors and skull fractures. MRI uses radio waves to create more detailed images, revealing bleeds, tumors and crude structural damage, but it cannot detect broken nerves. Even functional MRI (fMRI), which measures brain activity by tracking blood flow, can't detect the loss of neurons.

Like 5.3 million Americans living with TBI-related disabilities, Tom is tormented by injuries that are invisible to doctors. Robbed of his skills, he's been unable to work, throwing him into a downward socioeconomic spiral. Friends and family have quietly retreated, bewildered by his often inappropriate and emotional behavior, unable to recognize the man they once knew.

After talking with the lawyer, Karen eventually connected with a University of Pittsburgh research team working on a new brain imaging technique. In 2012, Tom set an appointment with neurosurgeon David Okonkwo, a professor of neurological surgery and the clinical director of the university's Brain Trauma Research Center. Brain and spinal cord injuries are his specialty. Okonkwo scheduled a two-hour brain scan for Tom in a high-powered MRI machine. He then asked him to return a couple of weeks later for the results.

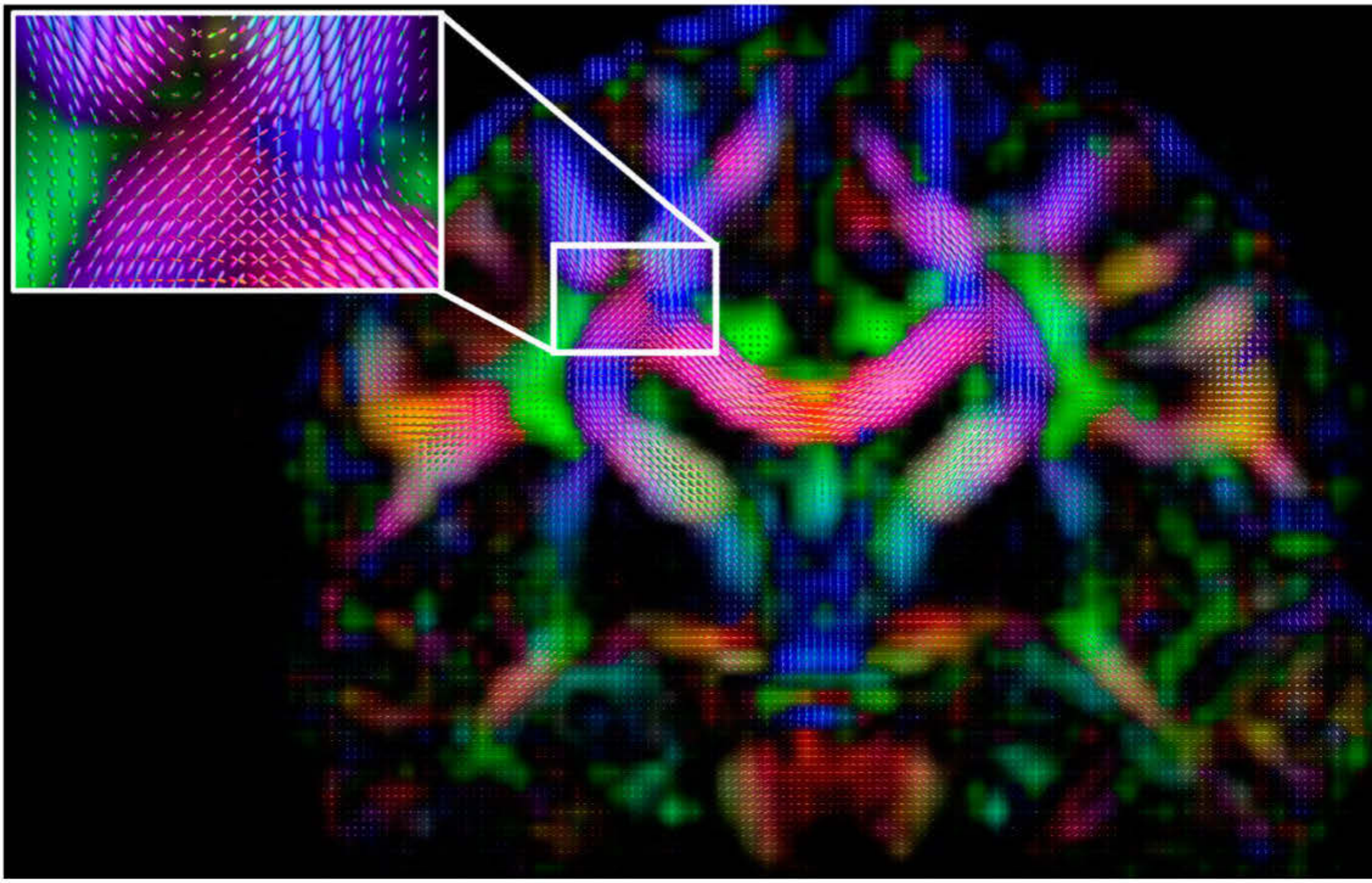
## NEURONS IN HIGH-DEF

Okonkwo knew that brain injuries were easily overlooked. Even today, when a head injury or coma patient is brought to the ER, the person gets a CT scan to determine if there is a blood clot in the brain that requires surgery. The problem, says Okonkwo, is that in nine out of 10 cases, those patients have a normal CT scan and are told they're fine. "But in many cases, they are not normal," he adds. "And they will be the first ones to share with you three months, six months later, the ways in which their life has changed." He says that in most hospitals, trying to diagnose a TBI is pretty much like trying to find a bone fracture before X-ray machines were invented.

But that changed for Okonkwo in fall 2009 when Walt Schneider, a lanky, snowy-haired psychologist, visited from across campus. Schneider is fascinated by technology, and he'd come to talk about a new way to image the major tracts of the brain. Tracts are bundled cables of axons that link one region of the brain to another — like superhighways — and conduct information. An axon is the long, skinny "tail" of a nerve cell, or neuron, that transmits electrical signals from one neuron to another elsewhere in the brain. Within a specific tract, all the nerve cells begin in the same location and end in a common location. Each tract has a predominant function: The corticospinal tract controls movement; the cingulate tract, memory; and the arcuate handles language. When an axon is injured, communication between particular neurons is lost; when an entire tract is severed, two brain regions can no longer talk to each other.

Schneider wanted a type of imaging that could produce a wiring diagram of all the neurons in the brain. But the current technology — diffusion MRI, also called diffusion tensor imaging (DTI) — didn't allow him to see injured axons that might explain the problems of TBI patients.

Traditional DTI uses magnetic pulses to tag water molecules in the nerve cells of the brain and then records



**A diffusion spin diagram reveals how water molecules move in a human brain. Restrictions in the motion and speed of the molecules give researchers clues to identify larger brain tracts, or bundles of axons that link one brain region to another. The inset shows an intersection of three major tracts.**

six characteristics of how these water molecules behave. The measurements are used to build images that trace the shape and direction of the axons and how the neurons in one region are connected to other brain regions. But DTI imaging had a major glitch: When axons from different tracts intersected and crossed en route to their target, the DTI software got confused and couldn't determine each tract's direction with complete accuracy. Schneider needed a technology that could follow these tracts from beginning to end.

With financing from the Defense Advanced Research Projects Agency, Schneider launched the 2009 Pittsburgh Brain Competition to lure the best minds to work on brain connectivity mapping. He offered $10,000 to anyone who could use data from a one-hour MRI scan to create a detailed image of the optic radiations — brain structures well defined through dissections. Teams from 168 countries signed on. As the results filtered in, Schneider's team found that most entries were just incrementally better than standard DTI imaging. But then a Taiwanese graduate student, Fang-Cheng Yeh, sent a stunning image. His work revealed Meyer's loop, a structure in the optic radiation, which no other team had successfully visualized. Yeh collected the reward, and Schneider enticed him to come to the U.S. to study. He worked with Schneider as part of his Ph.D. studies and is now a postdoctoral researcher at Carnegie Mellon University.

Sudhir K. Pathak, a mathematician and computational bioengineer in Schneider's lab, analyzed Yeh's approach. The key, Pathak found, was Yeh's use of more and sharper observations of water molecules (257 compared with the usual six) inside the nerve cells to figure out how the axons formed neural circuits in the brain.

"MRI only sees the water," explains Pathak. "By watching how the water moves, we can tell whether it's moving freely in all directions or if there is something restricting movement, like a nerve cell." Pathak improved versions of Yeh's algorithms, producing better and higher-resolution images, and then applied the approach to the entire brain to identify and map all 40 major brain tracts. Schneider and Pathak call this new method high definition fiber tracking (HDFT). Finally, to make the wiring diagram accessible, Pathak segmented and colored major pathways involved in various neural circuits in psychedelic hues.

Pathak spent the next year vetting the new brain images with Juan Fernandez-Miranda, a Pittsburgh neurosurgeon and neuroanatomist. He wanted to confirm that the virtual tracts he created on his computer screen matched those that the doctor saw during surgery. Fernandez-Miranda edited the images, pointing out when they were correct and when they took a wrong turn. The collaboration created a tenacious feedback cycle in which Pathak tuned the mathematics to create a tract, then Fernandez-Miranda

identified what was anatomically correct. Finally, Pathak's non-invasive virtual dissection rivaled Fernandez-Miranda's own bloodier one.

Okonkwo immediately saw the implications and began collaborating with Schneider to test the technology in a research trial by recruiting patients with brain injuries.

Pathak and other members in Schneider's lab then worked with Okonkwo and Fernandez-Miranda on an iPad app to create a tool that was clinically relevant and useful to neurosurgeons as they performed brain surgery or searched for damage in an injured patient.

Even today, when a head injury or coma patient is brought to the ER, the person gets a CT scan to determine if there is a blood clot in the brain that requires surgery. The problem is that in nine out of 10 cases, those patients have a normal CT scan and are told they're fine.

**VISUALIZING THE DAMAGE**

Two weeks after the scan, Tom and Karen sat with Okonkwo in an office at the University of Pittsburgh Medical Center Presbyterian. It was September 2012, more than three years since his fall. Tom hoped to hear a conclusive diagnosis, an anatomical explanation for his troubles and the rehabilitation strategy. He had been haunted by memories of the man he was before the accident, and he longed to be himself again.

Using his iPad, Okonkwo pulled up an image of Tom's brain. Each of the tracts was brightly colored, and looping, twisting and crisscrossing like a whorl of spaghetti.

On the screen, the left side of Tom's brain was green and the right side, red. There tends to be a natural symmetry between the two halves of the brain, and asymmetry makes us suspicious, Okonkwo explained. Although it could be due to a natural difference between the left and right hemispheres, it might indicate an injury where circuits have been disrupted. In some regions of Tom's brain, Okonkwo added, the circuits were asymmetrical.

He clicked on a drop-down menu and selected Tom's Papez circuit, which is key to the control of emotions and memory. "The right side of the brain doesn't have as much connectivity within the Papez circuit as the left side." The right side is the one that smacked the ground.

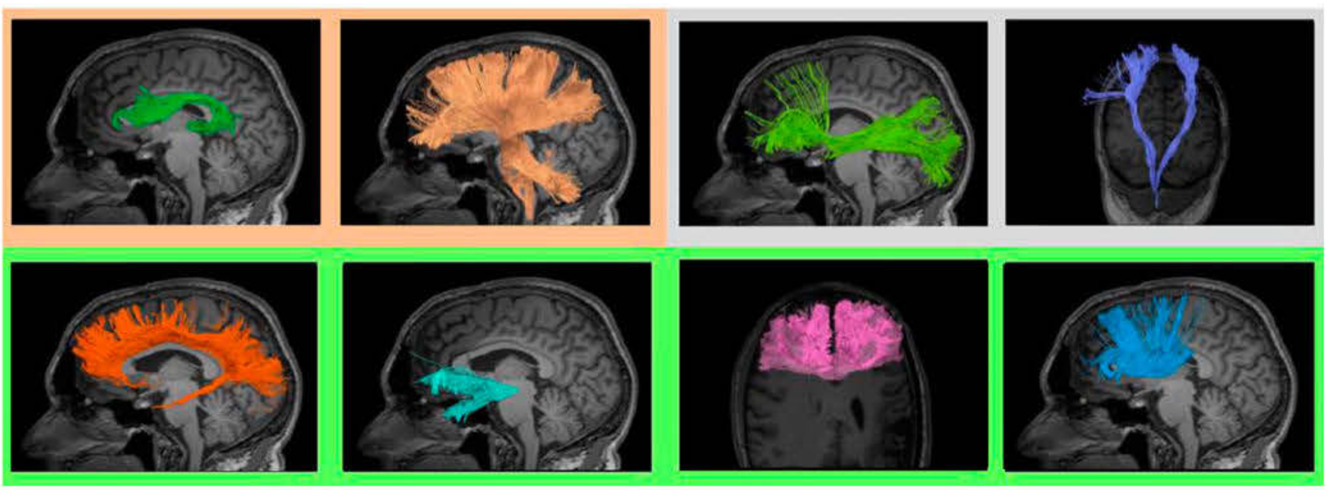
Okonkwo explained that networked connections can be lost. If, for example, the links from the eye to the back of the brain are reduced or severed, it may diminish vision. "That concept is true for the motor system, for the sensory system, and it's true in a slightly different way for memory, emotion, mood control," he said. Some of Tom's Papez circuit connections had been interrupted.

"The part of your brain responsible for encoding new memories isn't what it once was," said Okonkwo. He paused to let Tom digest. "And it can also be related to emotional stability and things like that."

Karen covered her face and started to cry. For the first time, after years of doubt, anxiety and frustration, they saw the broken cables in Tom's head. Okonkwo showed Tom another damaged brain circuit, the supplemental motor area, which is vital for integrating individual movements to make them smooth. The right side was dramatically different from the left, like someone arbitrarily hacked off huge branches of a tree. "It's very difficult to be graceful when you have trouble with the supplemental motor area. Does that sound like you?" Tom nodded.

Okonkwo stressed that the implications of the damage were unclear; this research was in its infancy. He told them that thousands of damaged brains must be scanned before doctors understand how various injuries affect brain function.

There's no obvious cure or therapy for Tom. But for Tom and Karen, just seeing proof that validates his symptoms felt like a step forward. "[It's] satisfying. Sad. Scary. Heartbreaking," said Karen. "It's given us a confirmation



ALL IMAGES: WALTER SCHNEIDER LABORATORY

**With high-definition fiber tracking, physicians can show patients the relative health of the major tracts in their brains. Colored borders are used as an aid to show those tracts with moderate injury concern (upper left), possible concern (upper right) and those within a normal range (across bottom).**

that I'm not crazy," Tom added. "For a long time, I thought I was losing my mind. Now I can finally move on."

Seeing a detailed scan of the brain is clinically important, both in a diagnostic sense as well as a therapeutic one, says Okonkwo. "There's actually someone who believes them."

For the past four years, Schneider and Okonkwo have been tweaking the technology. While they are enthusiastic and hopeful about their approach, others are more cautious. Arthur Toga, director of the Laboratory of Neuro Imaging at the University of Southern California, says there are still many unknowns when it comes to the brain, questions that he and others are trying to answer as part of the national brain mapping initiative called the Human Connectome Project. Many brain circuits are not symmetrical, and simply comparing the right and left halves to detect brain damage may not be reliable. He is also concerned that telling someone the degree of damage may not be helpful. "We don't know whether it is possible to recover those connections with the right treatments and rehabilitation strategies," says Toga.

"Walt's work is really promising, but it's definitely controversial," says Peter Bandettini, who specializes in fMRI as director of the fMRI facility at the National Institute of Mental Health. Others in the field doubt whether Schneider's methods can truly quantify damage to specific fiber tracts, he says. For example, can his approach really determine that 78 percent of the fibers in a particular tract have been destroyed? "The jury's still out on that."

But Bandettini supports Schneider's approach. "It's important for Walt to thrash this out, push the technology and see what it can do . . . [and] he's one of the few in brain imaging who is collaborating with the military and TBI doctors on clinical applications."

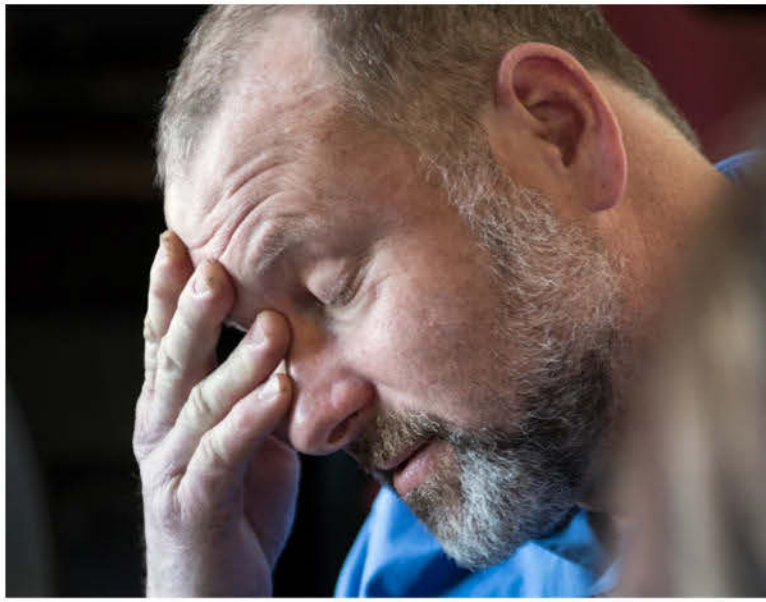
**"ACTIONABLE INTELLIGENCE"**

Part of that process is building the technical infrastructure that will allow Okonkwo and Schneider to better acquire MRI data, analyze and interpret it, and present brain images to clinicians and patients in a way that's intuitive. The scan now takes 22 minutes, the analysis just four hours.

Currently the only way to get a high-definition scan of brain fibers is to participate in a research trial. That will remain true for the next three to five years until the FDA approves the technology. But already, Okonkwo and Schneider are glimpsing the fruits of their efforts: They're helping patients understand the consequences of their brain injuries.

Treatment has been a national priority after military service in Afghanistan and Iraq resulted in a vast number of TBI and PTSD cases. Since 2007, the Department of Defense Combat Casualty Care Program has spent more than $700 million on 500-plus TBI projects, including $10 million from the U.S. Army Medical Research and Material Command for Schneider's technology. For Col. Dallas Hack, a physician and the brain health/fitness research coordinator at Fort Detrick, Md., the advantage of Schneider's HDFT technology is the ability to see and quantify the damaged circuits. He can use that to guide rehabilitation for the thousands of soldiers who've been through brain-rattling explosions.

> "My visual tracts that connect the brain to my eyes have taken a beating, which explained to me why I can't read. I'm not an idiot. I just have these cables that aren't working as well because a lot of them have been destroyed."
>
> — U.S. Army Special Forces soldier

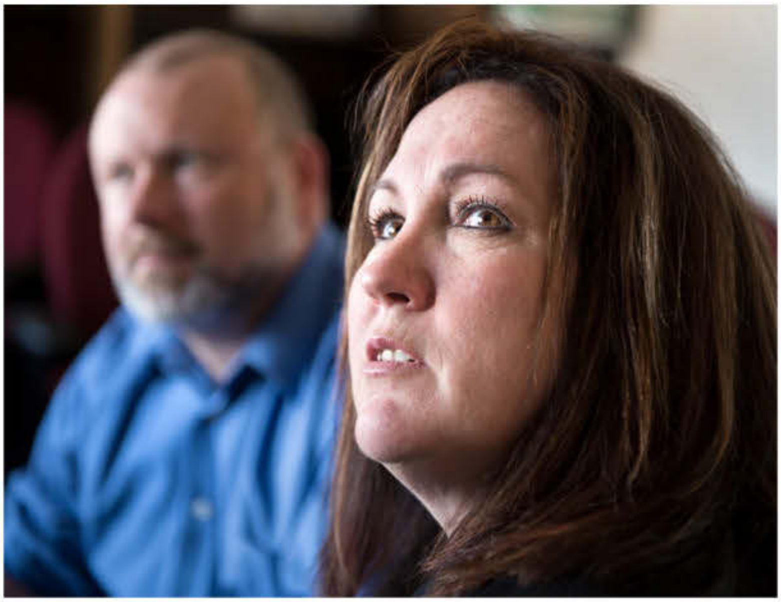


For one 46-year-old soldier (who asked that his name not be used because of the nature of his work), participating in Schneider's research trial has changed his life. He's spent more than 20 years in the U.S. Army Special Forces infantry division and has served in both Afghanistan and Iraq. After surviving some 400 explosions, he had memory lapses and attention deficits that he knew compromised his ability to lead high-altitude parachute missions into enemy territory — his specialty.

An exam confirmed short-term memory loss, but the problem ran deeper. He used to be a voracious reader and was fluent in several languages. Now he could barely get through an email, written words lost their meaning, and the languages blended unintelligibly in his head.

After the scan, Okonkwo showed him the source of his problems. "My visual tracts that connect the brain to my eyes have taken a beating, which explained to me why I can't read," he says. "I'm not an idiot, I'm not completely broken. I just have these cables that aren't working as well because a lot of them have been destroyed."

Although a rehabilitation strategy wasn't clear, in a moment of medical inspiration, one of Schneider's team



Tom Freund and his wife, Karen, listen as Pittsburgh researcher Schneider explains how high-definition fiber tracking helped identify damage to areas in Tom's brain. That visualization was the "last piece of the puzzle," Karen says, and helped them cope with changes in his behavior.

members recommended that he read to a beat — specifically using music, rhythm and doing something physical, such as tapping the words. They thought it might possibly retrain his brain to use other intact pathways.

He had nothing to lose. So he plugged in his headphones, set a beat and read his emails or had the computer read them as he looked at the words. It worked. When he's reading, he says, "I look like I'm cutting a rap record. I'm in the studio, it's me and Jay-Z, and we're getting it done!" That said, it takes longer, requires technology, and it's still not easy. "[But] I can read articles, emails, and I can read a book." This is all possible, he says, because he had an anatomically accurate scan that revealed which brain pathways were still viable.

With this new technology, the damage is now visible, and that's "actionable intelligence," says Schneider, who's fond of military jargon. "In a decade, we may know how to repair the damage much more effectively."

Scans done during and after rehabilitation and the use of various medications will prove whether damaged nerves can be repaired — and might begin to reveal how that happens.

Schneider's brain scanning technology is the closest to deployment, says Hack. The advantage of this technique is the images can be processed on machines currently used at major VA, DOD and medical centers around the country. As the TBI study expands, Schneider expects to scan more than 1,000 patients in the next three years at major hospitals in the Defense Department's Tricare health care program and at VA hospitals in Houston, San Diego, Tampa, Palo Alto, Calif., and Richmond, Va.

Schneider's fiber tracking images are similar to those emerging from the federally funded Human Connectome Project, which is mapping neural networks with DTI and generating its own stunning collection of Technicolor maps. "[But] Walt is one step ahead of [that] project," says Lawrence Wald, an investigator in the Massachusetts General Hospital-University of California Los Angeles consortium of the connectome project who also is collaborating with Schneider's team. The Connectome project has focused almost entirely on imaging the brains of healthy adults to provide a "gold standard" baseline for understanding diseased or injured brains. But Schneider has developed tools specifically for TBI, says Wald, and he has assembled a multidisciplinary team of clinicians, neurosurgeons and neuroanatomists to vet the images and identify and interpret wiring differences that are clinically significant.

SCOTT GOLDSMITH (3)

## A NEW CONNECTION

Two years after seeing the damaged cable, Tom and Karen seem at ease. For Karen, a definitive diagnosis provided "the last piece of the puzzle," she says. Understanding the reason behind Tom's behavior has helped her adjust, as well as heal their marriage.

The diagnosis also has made an important practical impact. Tom has undergone more cognitive and behavioral tests and is still working with several doctors. Workers' compensation is now picking up the medical bills, which had essentially wiped out his savings. Now getting the bills paid is not a constant fight.

"Since the diagnosis, it seems they genuinely want to help me," he says.

Karen still shares a special connection with Tom, but she admits that life has changed. "The Tom I know now is different. I have changed to coexist with him." She now has a better sense of what she can expect from him, and that understanding has been freeing for both of them. "Even though it was bad news, understanding the damage to Tom's brain was the answer to our prayers." D

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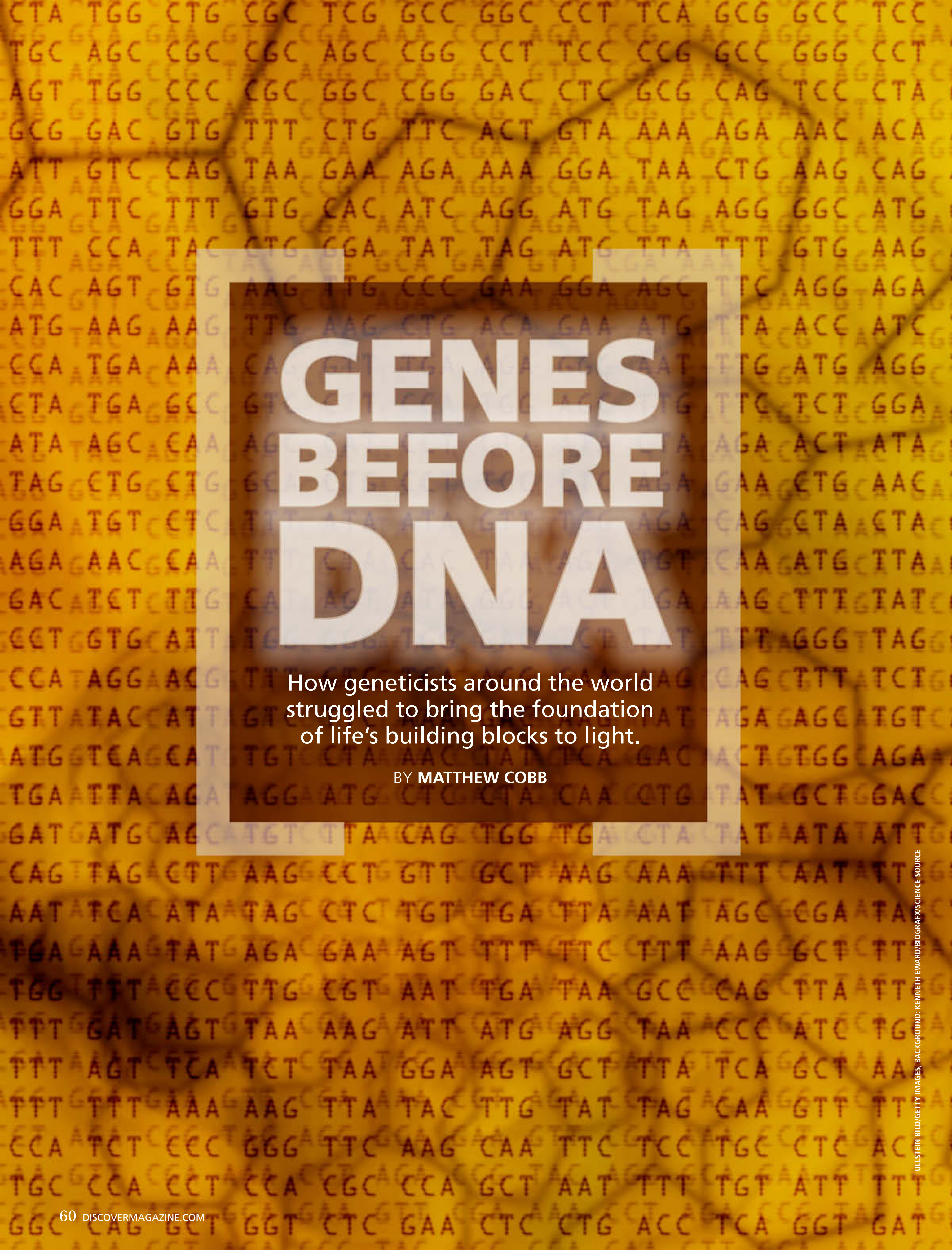
***Bijal P. Trivedi*** *is an award-winning freelance writer who covers medicine, genomics, health and nutrition. She lives in Washington, D.C.*

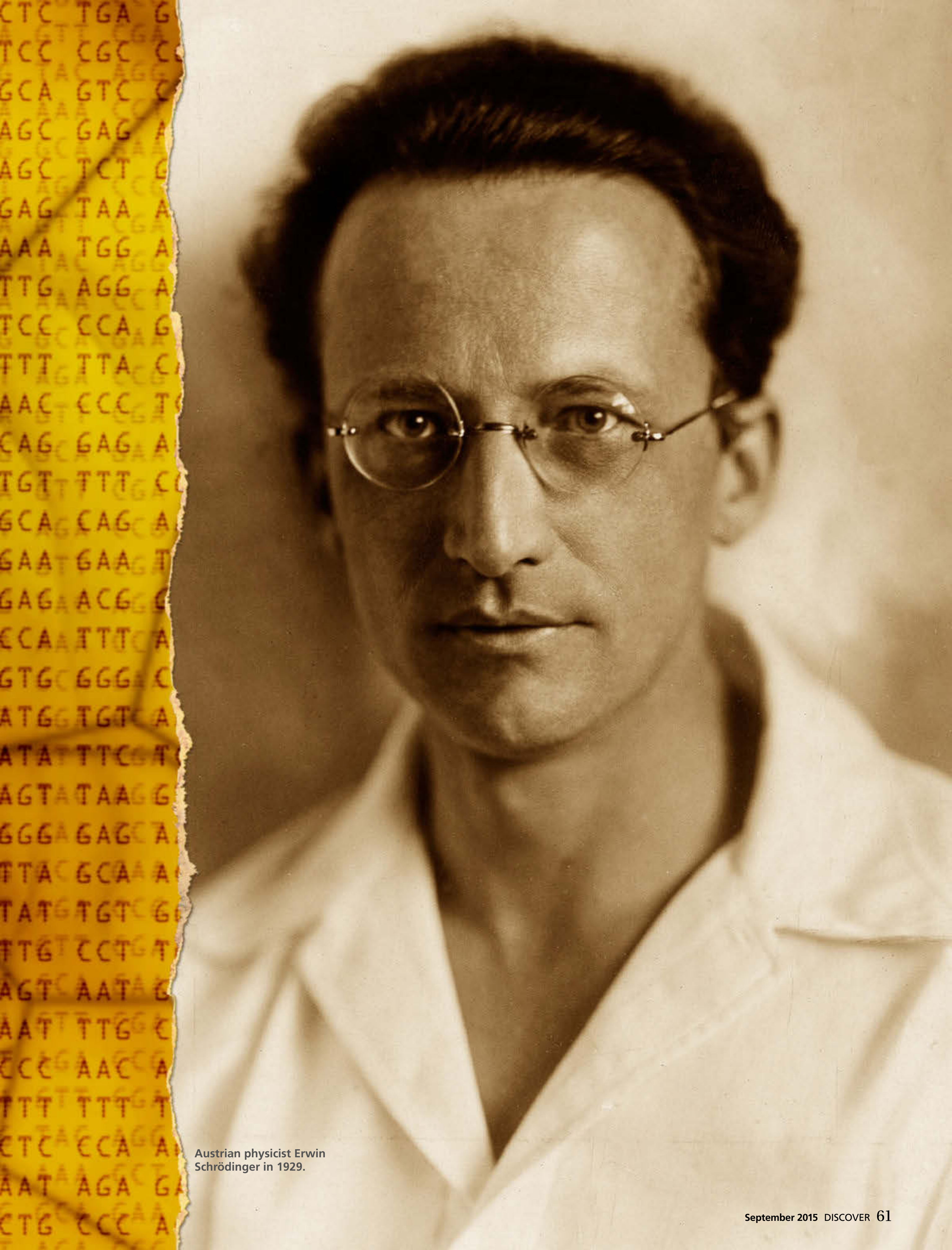


# GENES BEFORE DNA

How geneticists around the world struggled to bring the foundation of life's building blocks to light.

BY **MATTHEW COBB**

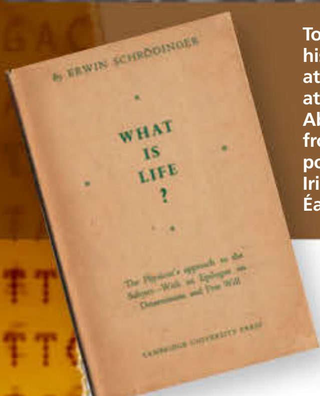
ULLSTEIN BILD/GETTY IMAGES; BACKGROUND: KENNETH EWARD/BIOGRAFX/SCIENCE SOURCE



Austrian physicist Erwin Schrödinger in 1929.

Trinity College sits in the heart of Dublin, its gray, three-story, neoclassical buildings positioned around lawns and playing fields. At the eastern end of the campus is another gray building, built in 1905 in a rather different style. This is the Fitzgerald Building, or the Physical Laboratory as it is called in deeply engraved letters on the stone lintel. On the top floor is a lecture theater, and in the late afternoon of the first Friday of February 1943, around 400 people crowded onto the varnished wooden benches.

According to *Time* magazine, among those lucky enough to get a seat were "Cabinet ministers, diplomats, scholars and socialites," as well as the Irish prime minister, Éamon de Valera. They were there to hear the Nobel Prize-winning physicist Erwin Schrödinger give a lecture with the intriguing title "What Is Life?" The interest was so great that scores of people were turned away, and the lecture had to be repeated the following Monday.




Top: Schrödinger gave his "What Is Life?" lectures at the Fitzgerald Building at Trinity College in Dublin. Above: Seated second from the right, Schrödinger poses with peers and Irish Prime Minister Éamon de Valera, far left.

An original copy of Schrödinger's book *What Is Life?* based on the popular, compelling lectures he gave in Dublin.

Schrödinger arrived in Dublin after fleeing the Nazis — he had been working at Graz University in Austria when the Germans took over in 1938. Although he had a reputation as an opponent of Hitler, Schrödinger published an accommodating letter about the Nazi takeover, with the hope of being left alone. This tactic failed, and he had to flee the country in a hurry, leaving his gold Nobel medal behind. De Valera, who was interested in physics, offered Schrödinger a post in Dublin's new Institute for Advanced Studies. And so the master of quantum mechanics found himself in Ireland.

On three consecutive Fridays, 56-year-old Schrödinger walked into the Fitzgerald Building lecture theater to give his talks, in which he explored the relationship between quantum physics and recent discoveries in biology.

## HEREDITY VS. PHYSICS

One of the topics he tackled was the nature of heredity. Like others before him, Schrödinger was struck by the fact that chromosomes are accurately duplicated during ordinary cell division (mitosis, the way in which an organism grows) and during the creation of the sex cells (meiosis). For your body to reach its current size, there have been trillions of mitotic cell divisions. And through all that copying and duplicating, the code has apparently been reliably duplicated. Furthermore, genes are reliably passed from one generation to another: Schrödinger explained to his audience that a well-known characteristic such as the Hapsburg, or Habsburg, lip — the protruding lower jaw shown by members of the House of Hapsburg — can be tracked over hundreds of years, without apparently changing.

For biologists, this apparently unchanging characteristic of genes was simply a fact. However, as Schrödinger

Top to bottom: Charles V, Rudolf II and Charles II have protruding lower jaws, called the Hapsburg lip.

explained to his Dublin audience, it posed a problem for physicists.

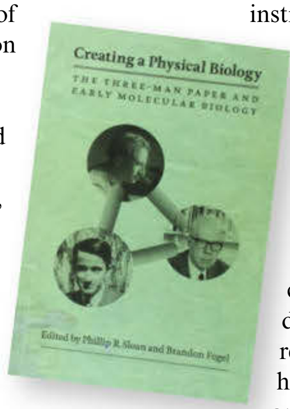
Schrödinger calculated that each gene might be composed of only 1,000 atoms. In that case, genes should be continuously shimmering and altering because the fundamental laws of physics and chemistry are statistical; although atoms overall tend to behave consistently, an individual atom can behave in a way that contradicts these laws. For most objects that we encounter, this doesn't matter. Things such as tables or rocks or cows are made of so many gazillions of atoms that they don't behave in unpredictable ways. A table remains a table; it does not spontaneously start to turn into a rock or a cow.

But if genes are made of only a few hundred atoms, they should display exactly that kind of uncertain behavior, and they shouldn't remain constant over the generations, argued Schrödinger. And yet experiments showed that mutations occurred quite rarely, and when they did happen, they were accurately inherited.

Schrödinger outlined the problem in the following terms:

*"Incredibly small groups of atoms, much too small to display exact statistical laws … play a dominating role in the very orderly and lawful events within a living organism. They have control of the observable large-scale features which the organism acquires in the course of its development; they determine important characteristics of its functioning; and in all this, very sharp and very strict biological laws are displayed."*

The challenge was to explain how genes act lawfully, and cause organisms to behave lawfully, while being composed of a very small number of atoms, a significant proportion of which may be behaving unlawfully. To resolve this apparent contradiction between the principles of physics and the reality of biology, Schrödinger turned to the most sophisticated genetic theory that existed at the time, proposed by Nikolai Timoféef-Ressovsky, Karl Zimmer and Max Delbrück.




## THE THREE-MAN PAPER

In 1926, Timoféef-Ressovsky, a Russian geneticist, collaborated with American geneticist Hermann Muller and showed that exposure to X-rays could induce mutations in genes. Shortly afterward, Timoféef-Ressovsky began a project with Zimmer, a radiation physicist, and Delbrück, a young German quantum physicist.

The trio decided to apply "target theory" — a central concept in the study of the effects of radiation — to genes. They bombarded a cell with X-rays to see how often different mutations appeared as a function of the radiation's frequency and intensity. By doing so, they thought it should be possible to deduce the physical size of the gene (the "target") and that measuring its sensitivity to radiation might reveal something about its composition.

The outcome of their collaboration was a joint German-language publication that appeared in 1935, called *On the Nature of Gene Mutation and Gene Structure*, more generally known as the Three-Man Paper.

The trio concluded that the gene was an indivisible physicochemical unit of molecular size, and they proposed that a mutation involved the alteration of a chemical bond in that molecule. Despite their best efforts, however, the nature of the gene, and its exact size, remained unknown.

In Dublin, as Schrödinger explored the nature of heredity for his audience, he was forced to come up with an explanation of what exactly a gene contained. But even the Three-Man Paper, the most advanced theory at the time, couldn't answer that question. And so, with nothing more than logic to support his hypothesis, Schrödinger argued that chromosomes "contain, in some kind of code-script, the entire pattern of the individual's future development and of its functioning in the mature state." This was the first time anyone clearly suggested genes might contain, or even simply could be, a code.

Taking his idea to its logical conclusion, Schrödinger argued that it should be possible to read the "code-script" of an egg and know "whether the egg would develop, under suitable conditions, into a black cock or into a speckled hen, into a fly or a maize plant, a rhododendron, a beetle, a mouse or a woman."

Although this was partly an echo of the earliest ideas about *how* organisms develop and the old suggestion that the future organism was preformed in the egg, Schrödinger's idea was very different. He was addressing the question of how the future organism was represented in the egg and the means by which that representation became biological reality. He was suggesting these were one and the same: The chromosome structures are instrumental in bringing about the development they foreshadow. They are law-code and executive power — or, to use another simile, they are like an architect's plan and a builder's craft — in one.

## SPEAKING IN CODE

To explain how his hypothetical code-script might work — it had to be extremely complicated because it involved "all the future development of the organism" — Schrödinger resorted to some simple mathematics to show how the variety of different molecules found in an organism could be encoded.

Schrödinger calculated that if each biological molecule was determined by a word of between one and 25 letters and the word was composed of five different letters, there would be 372,529,029,846,191,405 different possible combinations — far greater than the number of known types of molecule found in any organism. Having shown the potential power of even a simple code, Schrödinger concluded that "it is no longer inconceivable that the miniature code should precisely correspond with a highly complicated and specified plan of development and should somehow contain the means to put it into operation."

Although this was the first public suggestion that a gene contained something like a code, in 1892 a scientist named Fritz Miescher came up with something vaguely similar. In a private letter, Miescher argued that the various forms of organic molecules were sufficient for "all the

OPPOSITE, CLOCKWISE FROM TOP LEFT: THE BOARD OF TRINITY COLLEGE DUBLIN; YORCK PROJECT VIA WIKIMEDIA; WEB GALLERY OF ART VIA WIKIMEDIA; GRANGER NYC; AGSTRÖMER MEDICO-HISTORICAL LIBRARY; IRISH PRESS PLC

wealth and variety of hereditary transmission [to] find expression just as all the words and concepts of all languages can find expression in 24 to 30 alphabetic letters." Miescher's view can appear far-seeing, especially given that he was also the discoverer of DNA, or nuclein, as it was known at the time. But Miescher never argued that nuclein was the material making up these letters, and his suggestion was not made public for nearly 80 years. Above all, the vague letter-and-word metaphor was nowhere near as precise as Schrödinger's code-script concept.

Schrödinger then explored what the gene molecule might be made of and suggested that it was what he called a one-dimensional aperiodic crystal — a non-repetitive solid, with the lack of repetition being related to the existence of the code-script. The non-repetition provided the variety necessary to specify so many different molecules in an organism. Although Muller, American physicist Leonard Troland and Russian geneticist Nikolai Koltsov had all suggested two decades earlier that genes might grow like crystals, Schrödinger's idea was far more precise. His vision of gene structure was focused on the non-repetitive nature of the code-script, rather than on the relatively simple parallel between the copying of chromosomes and the ability of crystals to replicate their structure.

## BIG IDEA, LITTLE ATTENTION

Schrödinger's words would have had little influence had they simply hovered in the Dublin air and briefly resonated in the minds of the more attentive listeners. The sole international report to describe the lectures, which appeared in *Time* magazine in April, did not refer in detail to anything that Schrödinger said, and there are no indications that any of his ideas escaped to the outside world. The only detailed account appeared in *The Irish Press*, which managed to condense his main arguments and included both the code-script and aperiodic crystal ideas. Other newspapers found it difficult to give the story the attention it deserved; when Schrödinger gave a version of his lectures in Cork in January 1944, the local newspaper, *The Kerryman*, gave his talk equal coverage to the Listowel Pig Fair. (There was good demand for the 126 pigs on sale, they reported.)

Schrödinger felt the public would be interested in his views, and as soon as he finished the lectures, he began to turn them into a book, which was eventually published by Cambridge University Press in December 1944. The combination of Schrödinger's name, the intriguing title and a prestigious publisher with a global reach, coupled with the imminent end of the war, meant that the book was widely read and has remained in print ever since. Despite the commercial success of *What is Life?*, that was the end of Schrödinger's excursion into biology. He never wrote publicly on the topic again, even after the discovery of the existence of the genetic code in 1953.

The book's immediate impact can be seen from the enthusiastic reviews it received in both the popular press and in scientific journals. There were over 60 reviews in the four years after publication, although few writers noticed what now seem to be far-seeing ideas — the aperiodic crystal and the code-script — and it was translated into German, French, Russian, Spanish and Japanese.

There were two extended reviews in the leading scientific weekly *Nature*, one by geneticist J.B.S. Haldane, the other by the plant cytologist Irene Manton. Haldane got straight to the heart of the matter, picking up on the aperiodic crystal and the code-script innovations and making a link with the work of Koltsov. Manton also noted Schrödinger's use of the term *code-script*, but she took it to mean "the sum of hereditary material" rather than a particular hypothesis about gene structure and function. *The New York Times* reviewer put his finger on the central point:

> *"The genes and chromosomes contain what Schrödinger calls a 'code script,' that gives orders which are carried out. And because we can't read the script as yet, we know virtually nothing of growth, nothing of life."*

In contrast, some scientists later recalled they'd been unimpressed by the book. In the 1980s the Nobel Prize-winning chemist Linus Pauling claimed that he was "disappointed" on reading *What Is Life?* and stated, "It was, and still is, my opinion that Schrödinger made no contribution to our understanding of life."

Also in the 1980s, another Nobel laureate, biochemist Max Perutz, wrote of Schrödinger: "What was true in his book was not original, and most of what was original was known not to be true even when the book was written." In 1969, geneticist C.H. Waddington criticized Schrödinger's aperiodic crystal concept as an "exceedingly paradoxical phrase."

As well as these retrospective criticisms, some dissenting views were voiced when the book first came out. In a review, Delbrück was critical even though he received a publicity boost from Schrödinger's espousal of his work in the Three-Man Paper. He claimed Schrödinger's term *aperiodic crystal* hid more than it revealed:

> *"Genes are given this startling name rather than the current name 'complicated molecule.' … There is nothing new in this exposition, to which the larger part of the book is devoted, and biological readers will be inclined to skip it."*

This was distinctly ungenerous, as Schrödinger's hypothesis was, in fact, quite precise and did not simply involve coining a new name. Delbrück concluded by grudgingly accepting that the book "will have an inspiring influence by acting as a focus of attention for both physicists and biologists."

In another review, Muller said that he, too, expected the book would act as a catalyst for "an increasingly useful rapprochement between physics, chemistry and the genetic basis of biology." Muller clearly felt aggrieved that Schrödinger had not cited his work, and he pointed out that he had suggested the parallel between gene duplication and crystal growth in 1921 (though Muller decided not to mention that he took this concept from Troland). He also dismissed the idea that there was anything novel in Schrödinger's discussion of order and negative entropy, as these were both "quite familiar to general biologists." Neither Delbrück nor Muller made any comment about the code-script idea.

## INSPIRING NONETHELESS

Despite their overall skepticism, Delbrück and Muller were absolutely right: Schrödinger's book did indeed inspire a generation of young scientists. The three men who won the Nobel Prize for their work on the structure of DNA — James Watson, Francis Crick and Maurice Wilkins — all claimed that *What is Life?* played an important part in their personal journeys toward the double helix.

In 1945 Wilkins was handed a copy of *What is Life?* by a friend when he was working on the atomic bomb in California. Shaken by the horror of Hiroshima and Nagasaki, Wilkins was seduced by Schrödinger's writing and decided to abandon physics and become a biophysicist. Crick recalled that his 1946 reading of Schrödinger "made it seem as if great things were just around the corner." Watson was an undergraduate when he read *What is Life?* and as a result, he shifted his attention from bird biology to genetics.

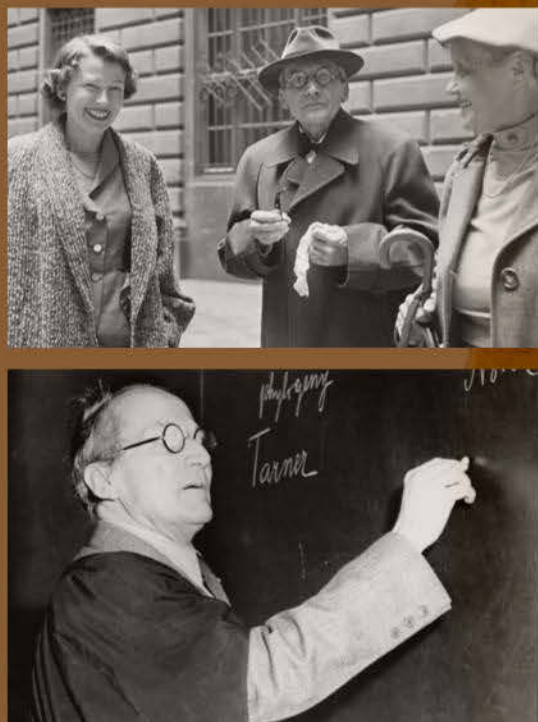
Even though some of the ideas developed in *What is Life?* were visionary and the book undoubtedly inspired some individuals who played a central role in 20th-century science, there are no direct links between Schrödinger's lectures and the experiments and theories that were part of the decades-long attempt to crack the genetic code, and historians and participants differ about the significance of Schrödinger's contribution.

The view of mutation put forward in the Three-Man Paper, which Schrödinger espoused so vigorously, had no effect on subsequent events, and his suggestion that new laws of physics would be discovered through the study of the material basis of heredity was completely mistaken. Even the code-script idea, which looks so prescient today, had no direct effect on how biologists looked at what was in a gene. None of the articles that later formed part of the discovery of the genetic code cited *What is Life?*, even though the scientists involved had read the book.

In fact, the meaning of Schrödinger's "code-script" did not have the same richness as our "genetic code." Schrödinger didn't think there was a correspondence between each part of the gene and precise biochemical processes, which is what a code implies. Nor did he address the issue of what exactly the code-script contained, beyond the vague suggestion of a plan.

Ask any biologist today what the genetic code contains, and they will give you a one-word answer: information. Schrödinger did not use that powerful metaphor. It was completely absent from his vocabulary and his thinking, for the simple reason that it had not yet acquired the abstract, wide-ranging meaning we now give it.

"Information" was about to enter science, but had not done so when Schrödinger gave his lectures. Without that conception of the content of the code, Schrödinger's insight was merely part of the zeitgeist, a hint of what was to come rather than a breakthrough that shaped all subsequent thinking. **D**




**After he fled to Ireland, Schrödinger lectured on the possible roots of heredity. He later founded wave mechanics, developed Schrödinger's equation and became the chair of physics at the University of Vienna.**

TOP: IMAGNO/GETTY IMAGES, BOTTOM: SSPL/GETTY IMAGES

Excerpted from *Life's Greatest Secret: The Race to Crack the Genetic Code* by Matthew Cobb. Available from Basic Books, a member of The Perseus Books Group. Copyright © 2015.

# Gut Reaction

To discover the evolution of the bacterial residents we host, a new field of research delves deep into unexpected corners of our fossil record.

BY **ADAM HADHAZY**

Recent Ph.D. graduate Andrew Ozga (standing) and current grad student Dave Jacobson prepare samples for analysis at the University of Oklahoma's ancient microbiome lab.

In the gleaming new Laboratories of Molecular Anthropology and Microbiome Research, opened in 2014 at the University of Oklahoma, positive air pressure keeps out external contamination, and intense ultraviolet lamps are on standby to sterilize the lab between uses. The focus of work here is not for the squeamish: Lab co-directors Christina Warinner and Cecil Lewis Jr. are digging into fossilized feces and dental plaque from long-dead humans, seeking traces of DNA from the trillions of bacteria the bodies hosted in life — just like we do today.

Collectively known as the microbiome and located primarily in the large intestine, these cohabitants outnumber their host human cells at least 10 to 1. Although scientists have known of this bacterial horde for years, it's only recently that we've begun to understand its crucial role in human well-being. Some research has even suggested a link between off-kilter microbiomes and the increase in many

Coprolites, fossilized feces like this example from the Iron Age, can preserve evidence of a host's microbiome.

**We're now learning about the evolution of the 90 percent of us that isn't, well, us.**

"diseases of civilization," such as obesity, asthma and Type 2 diabetes.

Thanks to powerful gene-sequencing techniques developed in the past two decades during the race to decode the human genome, researchers are beginning to reconstruct what our ancestors' microbiomes looked like, potentially going back thousands of years. For the first time, we're learning about the evolution of the 90 percent of us that isn't, well, us.

### WHAT'S BUGGING US

Ancient DNA analysis of microbiomes is in the early stages, but numerous studies of the microbiomes of today's traditional societies hint at what researchers may find.

For instance, recent research strongly suggests that in modern urban populations, the human microbiome has undergone major changes since the Industrial Revolution. It's possibly due to the rise in processed food, along with widespread antibiotic drug use and sanitation, all of which curtailed our microbial exposure. "We have far less interaction with microbes than we used to," says Warinner.

Consider a March *Nature Communications* study by Lewis and Warinner's team at OU. They compared fecal samples, loaded with gut microbiome members, from three groups: Amazonian hunter-gatherers and Andean farmers, both living in Peru, and an industrialized population in the U.S. Each group possessed distinct microbiomes with varying types of bacteria, but the American population stood out for having both different and less diverse critters. This same trend has turned up in other studies of remote South American and

TOP: CHRISTINA WARINNER. BOTTOM: ANDREW OZGA

African populations as well. "If you look at the big jumps in the different microbiomes, it's not between hunter-gatherers and agriculturalists — it's between both of them and us, the industrialized," says Warinner.

An April study in *Science Advances* drove this point home: A separate team found the highest human microbiome diversity ever seen in an isolated Yanomami tribe, discovered by Westerners only in 2009 in southern Venezuela.

**An eighth-century coprolite from a cave in Mexico (right) provided the first evidence of an ancient human microbiome. Today, researchers look to the microbiomes of people still living in traditional societies, such as the Yanomami (below), for clues about the bacterial colonies of our pre-industrial ancestors.**

## BURIED BACTERIAL TREASURE

These studies of present-day bacterial diversity are valuable, but to tell the whole story of the human microbiome's evolution, researchers must turn to fossilized feces, or coprolites, and tartar caked onto ancient teeth.

Among human archaeological remains, coprolites can be a uniquely valuable record of ancient gut microbiomes — but they're rare to find. In typical, relatively humid and warm environments, stool quickly breaks down. Yet in cool, arid conditions, such as dry caves, excreted feces can preserve bacterial DNA for centuries.

In 2008, Lewis and a team analyzed two coprolites from a Mexican cave. The samples were found in a sandy heap, doubling as a refuse dump and burial site, and had been sealed with adobe mud. The coprolites' exquisite preservation allowed the scientists to make the first confirmation of an ancestral, distinctly human microbiome, dating back to about A.D. 700. "These bacteria were clearly members of the gut," Lewis says.

In 2012, analyzing two other coprolites from the same site, Lewis and colleagues found that the ancient Native American microbiomes overall corresponded to modern, rural examples from traditional peoples in Africa, but not to industrialized bowel bugs. The team was even able to estimate the age of one of the human hosts from one sample's recovered bacterial DNA. One coprolite contained high levels of *Bifidobacterium breve*, often found today in breast-fed infants, and microbes in the genus *Prevotella*, linked to a carbohydrate-rich diet. Children in rural Africa commonly have these microbes in abundance as well, suggesting that the Mexican coprolite may have been that of a young child.

**Researchers are beginning to reconstruct what our ancestors' microbiomes looked like, potentially going back thousands of years.**

Deciphering the microbiome of yesteryear can extend to human ancestors, too, even extinct hominins.

TOP: RAUL TITO. BOTTOM: ODAIR LEAL/REUTERS/CORBIS

Calculi built up on teeth from a medieval European skull (above) preserve evidence of oral bacteria. Researchers scrape it off for analysis just like today's dentists (left).

BOTH IMAGES: CHRISTINA WARINNER

Neanderthals hold the record for the oldest hominin coprolites to date, plopped 50,000 years ago in a fire pit in El Salt, Spain. The feces contained traces of fats typically produced during digestion by bacteria that are found in microbiomes of omnivores. In other words, it looks like our Neanderthal cousins were probably consuming meat as well as vegetables. Although this particular coprolite sample has not been probed for the identities of its resident bacteria, Warinner says, as only a scientist could about fossilized poop: "I'd love to analyze it."

**A TALE TOLD IN TEETH**

Unlike rare, serendipitous coprolites, teeth turn up all the time in archaeological skeletal finds. Tartar, also called calculus, accumulates on teeth throughout our lives, spackling over clinging oral bacteria and bits of food. "Calculus builds up kind of like an onion," says Warinner. "And what's extraordinary about it is, it actually fossilizes while you're still alive."

Calculus is tough stuff, as any dentist with their scraping tools can tell you. Like bone, it lasts for ages. "We can expect to find calculus even on very ancient samples," says Amanda Henry of the Max Planck Institute for Evolutionary Anthropology in Germany. Henry studies glasslike particles, known as phytoliths, from plants eaten by hominins and sealed in their teeth tartar. She has picked through calculus from the early hominin *Australopithecus sediba*, dating back 2 million years. Now Henry is collaborating with Warinner to try to recover DNA and RNA from these samples. The researchers are also scrounging around for proteins, which can linger 10 times as long as DNA in tartar and provide hints of microbiota signatures.

"At this point, we have tantalizing glimpses," says Warinner. For instance, a breakthrough 2013 study by Australian scientists compared modern dental calculus to that of a small set of European skeletons spanning some 8,000 years, from the Stone Age through the late medieval period. As with gut bacteria, the researchers found that, in general, our ancestors had higher levels of oral bacteria diversity than we do. They also found that the earliest hunter-gatherers sampled in the study, before the rise of agriculture, had fewer types of oral bacteria associated with gum disease and cavities than later individuals. As agriculture became widespread, calculus bacterial colonies shifted away from those of hunter-gatherers, and periodontal disease increased.

The study identified another significant change in oral bacteria: In the calculus of modern Australians sampled, the tooth decay-causing *Streptococcus mutans* was dominant — but not so in the earlier samples. The researchers suspect *S. mutans* became more prevalent as consumption of processed grains and sugars increased after the Industrial Revolution.

At this preliminary stage of ancient microbiome research, many findings make it sound like humanity has fallen from a primordial, pre-technological grace. But Lewis and Warinner agree it's way too early to dive into trendy paleo diets or consider abandoning unquestionably life-saving antibiotics. The overall evolutionary story of the human microbiome — and any cautionary tales therein — will likely prove as complicated as the rise of our species itself, for we are one and the same. "Only by exploring our microbiomes today and in the past," Warinner says, "can we fully understand what it means to be human." D

***Adam Hadhazy*** *is a freelance science writer based in New Jersey. He also frequently contributes to* BBC Future *and* Astrobiology Magazine.

# Revelations From a Frozen Virus

Blood samples from the 1950s help rewrite the history of an infectious disease.

BY JESSICA WAPNER

Even a scrap of old DNA can yield vital clues about the history of a disease. So when Oliver Pybus, an evolutionary biologist at Oxford University, heard about the short sequence of viral genome extracted from blood kept frozen for more than 60 years, he had to have it. With that genetic sliver, Pybus thought he could add a vital chapter to a story he has long sought to complete: the history of the hepatitis C virus.

Scientists have amassed a wealth of knowledge about hepatitis C since its discovery in 1989. The virus currently infects about 150 million people worldwide and exists in several variations, or genotypes. Roughly 3 million people are infected in the U.S., mostly as a result of blood transfusions before the mid-1970s, when paid blood donations were stopped. (People infected with hepatitis C, often through contaminated needles from injection drug use, accounted for a large swath of paid donors.)

The hepatitis C virus can remain silent for decades as it colonizes the liver and may never harm its human host. But in about a third of those infected, hepatitis C can cause cirrhosis, liver cancer and death if untreated.

After years of difficult and inadequate treatments, two drugs — Harvoni and Viekira Pak, approved in 2014 — eradicate the virus in more than 90 percent of patients (though their high cost — around $80,000 for a 12-week course of treatment — has come under continual fire).

Still, mysteries remain. No one knows the natural course of the disease over a human lifetime, or how the virus spread around the world in the first place. The virus mutates exceptionally fast — "a million times faster than our own genome," says Pybus.

Pybus studies the evolution of viruses using genetic sequences and computer software. Biologists have used mathematics to infer viral ancestry — turning back the molecular clock, they call it — since the 1960s. Based on coalescent theory, an approach to population genetics that uses genetic diversity to trace genealogies, Pybus developed calculations that generate approximate chronologies of viral epidemics. Equipped with nothing more than genomes and the rate of mutation — no blood samples or medical histories required — Pybus has uncovered the history of HIV, various flu viruses and other pathogens. His methods earned him some fame with the Centers for Disease Control and Prevention when he and others found the origin of the 2009 swine flu outbreak.

Like a viral cartographer, Pybus has also mapped the journey of hepatitis C from Ghana to the Caribbean along trans-Atlantic slave trade routes between 1700 and 1850, and from the Netherlands to Indonesia and Surinam during Dutch colonial rule. His calculations revealed the movement of hepatitis C from Central

Although discovered in 1989, the hepatitis C virus (top) has existed for much longer. Researchers have mapped its journey along 18th- and 19th-century slave trade routes.

TOP: RAMON ANDRADE/SCIENCE SOURCE. BOTTOM: DEA PICTURE LIBRARY/DEAGOSTINI/GETTY IMAGES

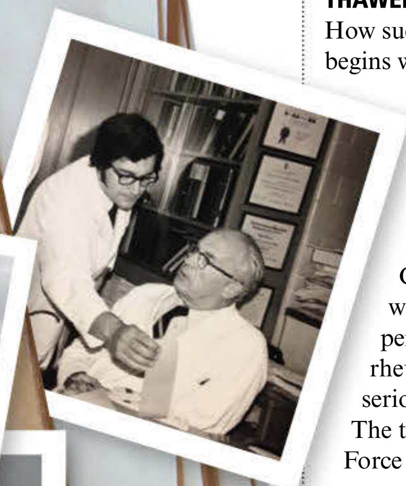
Africa to Egypt sometime between 1860 and 1925. Pybus theorized that Tunisian troops carried the virus home from the Democratic Republic of Congo after the United Nations stationed them there in the 1960s during the Congo crisis.

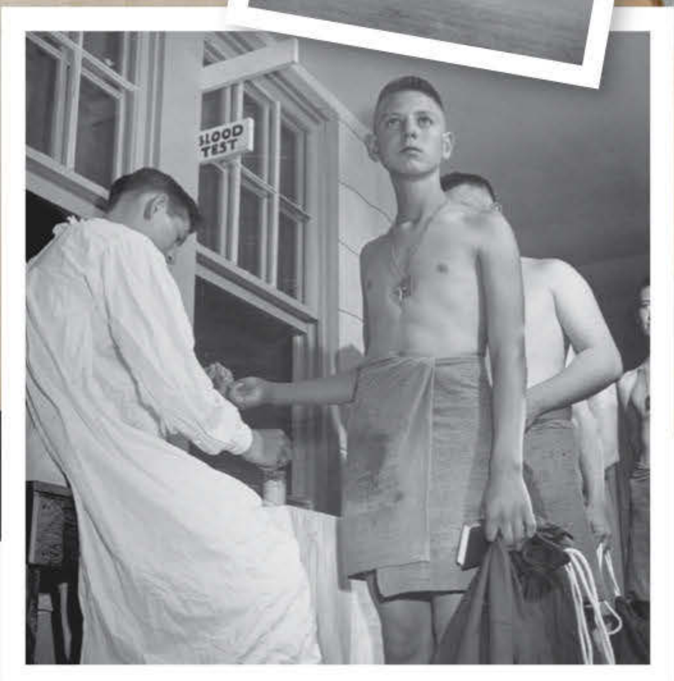
But the map is sketchy, owing to the lack of older evidence. The more recent the sequence, the less precise the history. Only older genomes could make the map more exact. And now Pybus had his most powerful tool yet: the oldest genetic evidence of hepatitis C.

A few of the 45,000 blood samples from recruits at Warren Air Force Base in the 1940s and '50s. Sixty years later, a genetic sequence extracted from these frozen samples would shed new light on the mystery of hepatitis C.

## THAWED RESEARCH

How such evidence became available begins with another infectious agent: *Streptococcus pneumoniae*, the bacterium that causes strep throat. In the mid-1940s, the Department of Defense commissioned researchers, led by infectious disease scientist Charles Rammelkamp, to study whether treating strep with penicillin would also prevent rheumatic heart disease, then a serious problem among troops. The team focused on Warren Air Force Base in Wyoming, where strep was common, collecting some 45,000 blood samples from more than 9,000 recruits between 1948 and 1954.






Charles Rammelkamp (above, seated) led the team at Warren AFB (upper left) that drew the thousands of samples that became the Warren Sera Collection.

FROM TOP: EDWARD KAPLAN AND DWIGHT JOHNSON (2); METROHEALTH SYSTEM ARCHIVE DEPARTMENT; LIBRARY OF CONGRESS; MICHAEL ROUGIER/THE LIFE PICTURE COLLECTION/GETTY IMAGES. BACKGROUND: VALENTIN AGAPOV/SHUTTERSTOCK

After they got their answer — yes, penicillin could prevent rheumatic heart disease — Rammelkamp, recognizing the samples' potential value to future research, kept the vials in basement freezers at Cleveland's Case Western Reserve University, where he held a professorship until retiring in the mid-1970s.

Rammelkamp's colleague, Edward Kaplan, a pediatric infectious disease specialist and pediatric cardiologist at the University of Minnesota Medical School, then took the baton. "It's a priceless collection," he says, but its future was precarious; Kaplan knew the samples would be discarded if he didn't act to preserve them. And act he did:

The resourceful Kaplan got a local trucking concern to transport the vials from Cleveland to Minneapolis in a frozen pizza truck for free, provided they could tout the contribution to medical research in their union magazine.

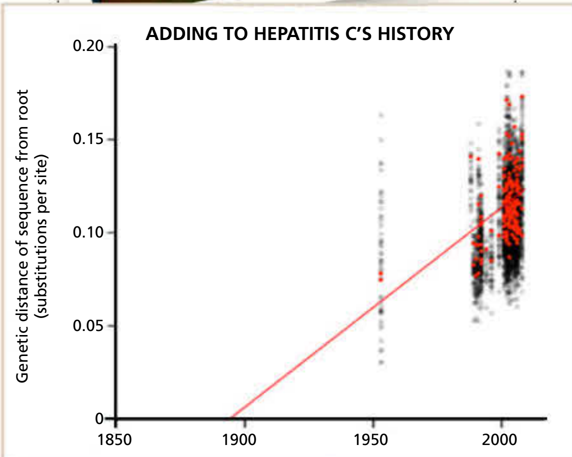
In the mid-1990s, Leonard Seeff, a hepatologist at the Veterans Administration Hospital in Washington, D.C., overheard Kaplan discussing the Warren Sera Collection, as it came to be known. Seeff immediately wondered whether any of the blood samples contained antibodies to the hepatitis C virus. If they did, Seeff could answer a question that had been impossible to investigate: How prevalent was hepatitis C in the 1940s and '50s before it was even known to exist? No one knew. But if the virus was present in these frozen samples, Seeff could study the 40-year course of the disease in an instant.

"He said if you find any positives for hepatitis C, I'll give you a bottle of champagne," Kaplan recalls.

The samples were defrosted for the first time in 40 years, and more than 8,500 army recruits were retroactively tested for the virus. Seventeen were positive. Hepatitis C had been at the Warren Air Force Base in the 1950s. And eight of those recruits were still alive.

Zelma Buskell, Seeff's study coordinator, traveled across the country to meet most of the veterans and take new samples. Not any of them knew how they got the virus, though one veteran remembered injecting drugs during that time, to Buskell's surprise.

"You think of drug use as starting with Vietnam," she says. Finding the recruits in generally good health contradicted the grim outlook most physicians held for hepatitis C patients. "People who'd been infected 40 years earlier were still alive," says Seeff, who reported his results in 2000. "It was not inevitably a fatal disease."




**Thanks to 1950s data provided by the Warren samples, evolutionary biologist Oliver Pybus was able to chart the genetic divergence of the post-1989 hepatitis C virus back to the turn of the 20th century.**

## A FIRST DATE

The story could have ended there, except for one inquisitive scientist at the National Institutes of Health. In 2001, Yasuhito Tanaka, now at Nagoya University, spent a year in the NIH laboratory of Harvey Alter, the virologist largely credited with the discovery of hepatitis C. Tanaka wanted to know when hepatitis C entered the U.S., so he asked Seeff for viral samples to sequence.

After making his way through just 4 percent of the viral genome, Tanaka found he couldn't complete the sequences and set the project aside. It was all but forgotten until Pybus heard about it in 2011 from another Japanese colleague and asked Tanaka to send what he had.

Pybus suspected his methods, unavailable just a few years earlier, could wring some vital history out of Tanaka's work. Tanaka had sequenced the middle region of the code for NS5B, the enzyme that makes new genome copies during replication. Pybus compared the sequences with genomes of modern-day hepatitis C virus. The number of differences between them, explains Pybus, "is indicative of how long it's been since they shared a common ancestor."

The study confirmed that the 1953 strain was genotype 1B, one of the epidemic subtypes of the virus and a common strain worldwide. Pybus then calculated when the sequences would have last been alike: in 1901, give or take about 25 years. "All subtype 1B infections today are descended from that one 1B infection back at the turn of the century," he says.

Pybus speculates that the virus first arrived in the U.S. decades earlier in the blood of West Africans sold into slavery. This route could explain why African-Americans were historically less responsive to some treatments for hepatitis C: The virus may have "increased its ability to infect and persist in individuals with that genetic background," he notes. Sequencing the rest of the 1953 genome samples could yield further insights, and Pybus also hopes to find more such ancient treasures, which help shed light on our genetic relationship with diseases.

As for Kaplan, he's still waiting for his bottle of champagne from Seeff. The blood samples he kept safe for so long are waiting, too. In 2009, Kaplan transferred the samples back to the care of the government. They currently sit frozen at Wright Patterson Air Force Base in Ohio, ready for the next researcher to defrost a mystery. D

*__Jessica Wapner__ is a New York-based writer and author of* The Philadelphia Chromosome: A Genetic Mystery, a Lethal Cancer, and the Improbable Invention of a Lifesaving Treatment. *Read her stories at __jessicawapner.com__*

TOP: EDWARD KAPLAN AND DWIGHT JOHNSON. BOTTOM: GRAY, ET AL. (2013) PHIL TRANS ROY SOC B 368:20130168

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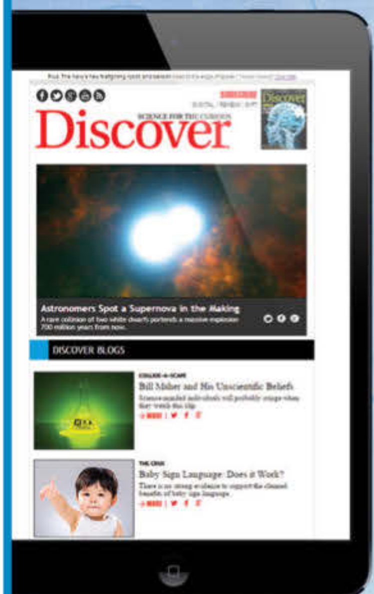


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# The Human Voice

BY **JIM SULLIVAN**

**1** For decades, scientists thought a key element of generating voice was the Bernoulli effect, the same change in relative air pressure that allows airplanes to fly and curveballs to befuddle batters. **2** We now know, however, that voice generation is far more complex. Muscles in the vocal folds provide resistance to air in the lungs. As air is exhaled, it pushes between the folds, which open and close rapidly. Air above the folds is alternately compressed and decompressed, creating sound waves. **3** Researchers at the National Center for Voice and Speech theorize that singing is a more right-hemisphere brain function, while speaking is more left-hemisphere dominant. **4** This dichotomy is why some victims of stroke, unable to speak, can still sing. **5** It's also why some famous singers — including Carly Simon, Mel Tillis and Bill Withers — ply their trade with no problem, but sometimes stutter in conversation. **6** Conversational voice is about 60 decibels, but the loudest human voice, according to *Guinness World Records*, belongs to teaching assistant Jill Drake of Kent, England. Her scream of 129 dBA was equivalent to noise levels at an AC/DC concert, and about 30 dB louder than a jackhammer. **7** The most complex language to voice is !Xóõ, spoken mostly in Botswana. It has 112 distinct sounds. English, by comparison, has about 40. **8** Tuva, as one might expect, is where Tuvan throat singing, or *Khöömei*, originated. The nomadic people of this small corner of Siberia prize multiple pitches in their music rather than single, clear tones. **9** Some throat singers can produce four tones simultaneously. **10** To understand throat singing technique, imagine bagpipes. Just as pipers first produce a low drone and then layer on additional tones, throat singers start with a droned vocalization and then manipulate their vocal folds, root of the tongue or epiglottis — a flap of cartilage at the base of the tongue — to add additional notes. **11** An entirely different sort of vocal manipulation, yodeling, is a fast alternation between low notes and falsetto. **12** Whether throat singing, yodeling or just plain speaking, there are more baritones among males than either basses or tenors. Similarly, the middle range — mezzo-soprano — is the most common of female vocals. **13** All children are considered trebles, with the same approximate range as a soprano. It isn't until puberty that both girls and boys experience a lengthening and thickening of vocal folds that change their vocal range, with males' folds becoming considerably longer and thicker than females'. **14** Well, usually, anyway. Castrati were male singers castrated before puberty. Without the normal adult male testosterone levels, they remained natural trebles. **15** Castrati were often highly paid, and in less enlightened times, some parents castrated their sons in hopes of cashing in. **16** The only surviving recordings of a castrato performing solo are from 1904 by Alessandro Moreschi. He hits notes common to a soprano with no apparent strain. **17** On the other end of the musical spectrum, the lowest note ever sung was a G (-7) (0.189 hertz) by singer Tim Storms. Eight octaves below the lowest G on a piano, the note is actually outside of human hearing. It was captured using a low-frequency microphone and then verified via precision sound analysis. **18** Storms also holds the Guinness record for widest range, a full 10 octaves — about twice that of Mariah Carey and more than three times the average singer's range of just three octaves. **19** In 1860, the phonautograph, invented by Édouard-Léon Scott de Martinville, captured the oldest recognizable recording of the human voice. Like Thomas Edison's later invention, the phonograph, Scott's phonautograph converted sound waves into lines traced onto a turning cylinder. **20** Unlike Edison, however, Scott never intended to play back his recordings: His goal was a visual representation of voice. Only with recently developed software could modern researchers hear his recording of a singer performing *Au Clair de la Lune*. D

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*In addition to his career as a writer,* ***Jim Sullivan*** *has done voiceover work for more than 20 years.*

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